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(54) **C13-HYDROXY DERIVATIVES OF OLEANOLIC ACID AND METHODS OF USE THEREOF**

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(52) **U.S. Cl.**

CPC ***C07C 255/47*** (2013.01); ***C07D 307/00*** (2013.01); ***C07J 63/008*** (2013.01)

(58) **Field of Classification Search**

CPC C07J 63/008; C07C 255/47; C07D 307/00
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See application file for complete search history.

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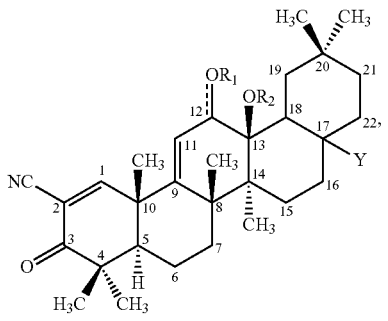
(57) **ABSTRACT**

Disclosed herein are novel C13-hydroxy derivatives of oleanolic acid, including those of the formula:

(I)



wherein the variables are defined herein. Also provided are pharmaceutical compositions, kits and articles of manufacture comprising such compounds. Methods and intermediates useful for making the compounds, and methods of using the compounds, for example, as antioxidant inflammation modulators, and compositions thereof are also provided.

24 Claims, No Drawings

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C13-HYDROXY DERIVATIVES OF OLEANOLIC ACID AND METHODS OF USE THEREOF

This application claims the benefit of U.S. Provisional Patent Application No. 61/699,182 filed on Sep. 10, 2012, the entirety of which is incorporated herein by reference.

Pursuant to 37 C.F.R. 1.821(c), a sequence listing is submitted herewith as an ASCII compliant text file named "REATP0078US_SequenceListing_ST25.txt", created on Sep. 10, 2013 and having a size of ~1 KB. The content of the aforementioned file is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of biology and medicine. More particularly, it concerns compounds, compositions and methods for the treatment and prevention of diseases such as those associated with oxidative stress and inflammation.

II. Description of Related Art

The anti-inflammatory and anti-proliferative activity of the naturally occurring triterpenoid, oleanolic acid, has been improved by chemical modifications. For example, 2-cyano-3,12-diooxooleana-1,9(11)-dien-28-oic acid (CDDO) and related compounds have been developed (Honda et al., 1997; Honda et al., 1998; Honda et al., 1999; Honda et al., 2000a; Honda et al., 2000b; Honda, et al., 2002; Suh et al. 1998; Suh et al., 1999; Place et al., 2003; Liby et al., 2005; and U.S. Pat. Nos. 8,129,429; 7,915,402; 8,124,799; 8,071,632; 8,338,618; and 7,943,778). The methyl ester, bardoxolone methyl (CDDO-Me), has been evaluated clinically for the treatment of cancer and chronic kidney disease (Pergola et al., 2011; Hong et al., 2012).

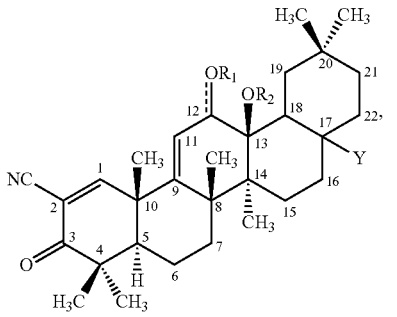
Synthetic triterpenoid analogs of oleanolic acid have also been shown to be inhibitors of cellular inflammatory processes, such as the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda et al. (2000a); Honda et al. (2000b), and Honda et al. (2002). Synthetic derivatives of another triterpenoid, betulinic acid, have also been shown to inhibit cellular inflammatory processes, although these compounds have been less extensively characterized (Honda et al., 2006). The pharmacology of these synthetic triterpenoid molecules is complex. Compounds derived from oleanolic acid have been shown to affect the function of multiple protein targets and thereby modulate the activity of several important cellular signaling pathways related to oxidative stress, cell cycle control, and inflammation (e.g., Dinkova-Kostova et al., 2005; Ahmad et al., 2006; Ahmad et al., 2008; Liby et al., 2007a). Derivatives of betulinic acid, though they have shown comparable anti-inflammatory properties, also appear to have significant differences in their pharmacology compared to OA-derived compounds (Liby et al., 2007b). Given that the biological activity profiles of known triterpenoid derivatives vary, and in view of the wide variety of diseases that may be treated or prevented with compounds having potent antioxidant and anti-inflammatory effects, and the high degree of unmet medical need represented within this variety of diseases, it is desirable to synthesize new compounds with diverse structures that may have improved biological activity profiles for the treatment of one or more indications.

SUMMARY OF THE INVENTION

The present disclosure provides novel synthetic triterpenoid derivatives, with anti-inflammatory and/or antioxidant properties, pharmaceutical compositions, and methods for their manufacture, and methods for their use.

In one aspect, there are provided compounds of the formula:

(I)



wherein:

R_1 is hydrogen, $alkyl_{(C\leq 6)}$, $acyl_{(C\leq 6)}$, or absent when the oxygen atom to which it is bound forms part of a double bond;

R_2 is hydrogen, $alkyl_{(C\leq 6)}$, $acyl_{(C\leq 6)}$, a substituted version of either of the two latter two groups, or as provide for below; and

Y is:

hydrogen, hydroxy, halo, amino, cyano or mercapto;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or substituted versions of any of these groups;

$-alkanediyl_{(C\leq 8)}-R_a$, $-alkenediyl_{(C\leq 8)}-R_a$, or a substituted version of any of these groups, wherein R_a is:

hydrogen, hydroxy, halo, amino, cyano or mercapto;

$heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, —OC(O)NH-$alkyl_{(C\leq 8)}$, —$OC(O)CH_2NHC(O)O$— $alkyl_{(C\leq 8)}$, —OCH_2-$alkylthio_{(C\leq 8)}$, or a substituted version of any of these groups; or

R_a and R_2, taken together, are a covalent bond between one end of the $-alkanediyl_{(C\leq 8)}-$ or $-alkenediyl_{(C\leq 8)}-$ group and the oxygen atom attached to the carbon atom labeled 13; or

$—(CH_2)_mC(O)R_b$, wherein m is 0-6 and R_b is:

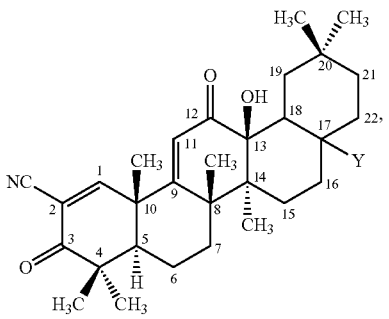
hydrogen, hydroxy, halo, amino, hydroxyamino, or mercapto;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, —NH-$heterocycloalkyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

R_b and R_2, taken together, are a covalent bond between the carbonyl of the $—(CH_2)_mC(O)—$ group and the oxygen atom attached to the carbon atom labeled 13, wherein m is 1-6;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(II)

wherein Y is:

hydrogen, hydroxy, halo, amino, cyano or mercapto;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or substituted versions of any of these groups;

-$alkanediyl_{(C\leq 8)}$-R_a, -$alkenediyl_{(C\leq 8)}$-R_a, or a substituted version of any of these groups, wherein R_a is:

hydrogen, hydroxy, halo, amino, cyano or mercapto; or

$heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, —$OC(O)NH$-$alkyl_{(C\leq 8)}$, —$OC(O)CH_2NHC(O)O$-$alkyl_{(C\leq 8)}$, —OCH_2-$alkylthio_{(C\leq 8)}$, or a substituted version of any of these groups; or

—$(CH_2)_mC(O)R_b$, wherein m is 0-6 and R_b is:

hydrogen, hydroxy, halo, amino, hydroxyamino, or mercapto; or

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, —NH-$heterocycloalkyl_{(C\leq 8)}$, or a substituted version of any of these groups;

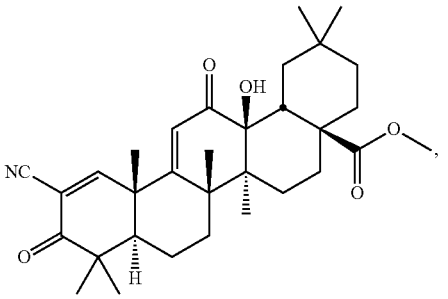
or a pharmaceutically acceptable salt thereof.

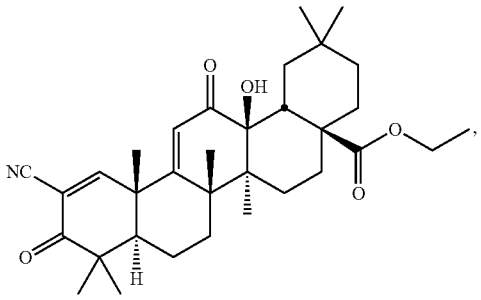
In some embodiments, R_1 is hydrogen. In other embodiments, R_1 is $acyl_{(C\leq 6)}$, for example, acetyl. In some embodiments, R_1 is absent and the oxygen atom to which it is bound forms part of a double bond, thereby resulting in an oxo group at the carbon atom labeled 12.

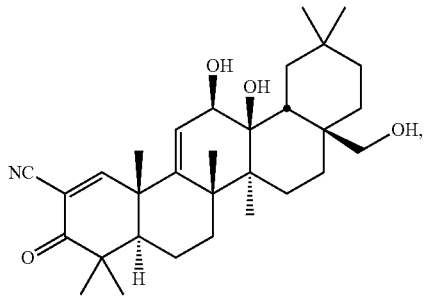
In some embodiments, R_2 is hydrogen.

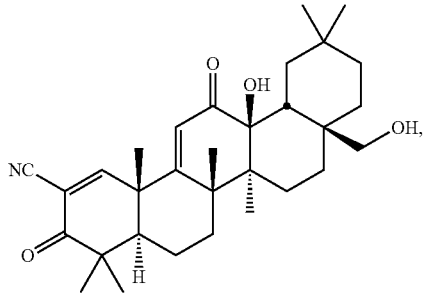
In some embodiments, Y is substituted $alkyl_{(C\leq 8)}$, for example, hydroxymethyl. In some embodiments, Y is -$alkanediyl_{(C\leq 8)}$-R_a, for example, —CH_2—R_a. In some embodiments, R_a is hydroxy. In some embodiments, R_a is $acyloxy_{(C\leq 8)}$, for example, acetyloxy. In some embodiments, Y is —$(CH_2)_mC(O)R_b$. In some embodiments, m=0. In some embodiments, R_b is $alkoxy_{(C\leq 8)}$, for example, methoxy or ethoxy. In some embodiments, R_b is amino. In some embodiments, R_b is $alkylamino_{(C\leq 8)}$, for example, ethylamino.

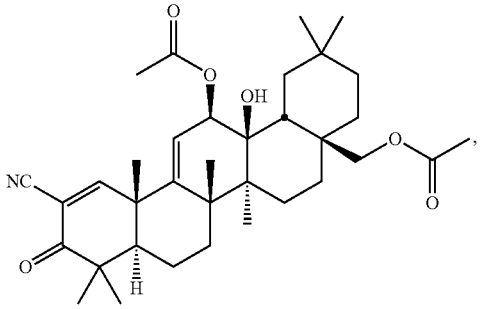
In some embodiments, the compound is selected from the group consisting of:











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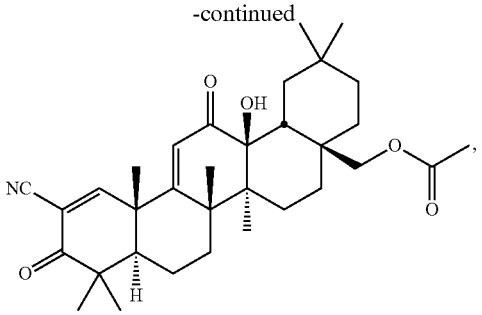
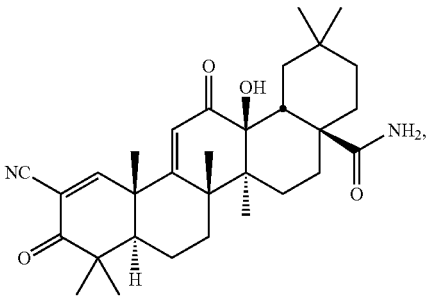
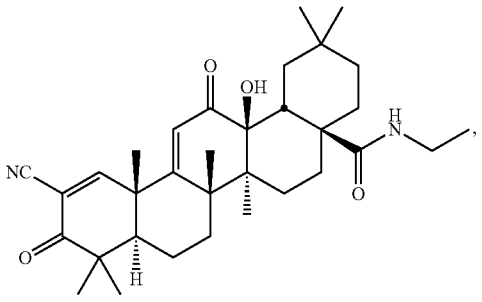
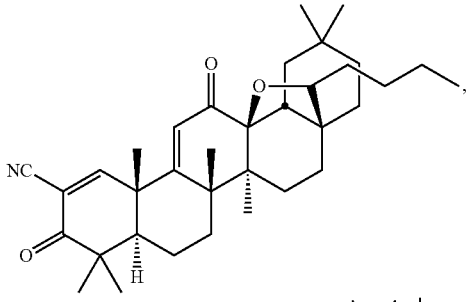
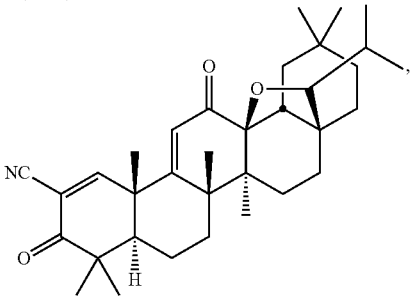








and



or a pharmaceutically acceptable salt thereof.

In some aspects, there are provided pharmaceutical compositions comprising one or more of the above compounds and an excipient. In other aspects there are provided methods of treating and/or preventing a disease or a disorder in patients in need thereof, comprising administering to such patients one or more of the above compounds in an amount sufficient to treat and/or prevent the disease or disorder.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula doesn't mean that it cannot also belong to another generic formula.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

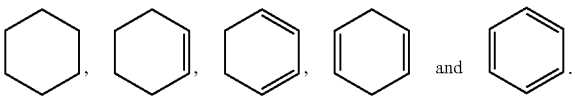
Disclosed herein are new compounds and compositions with antioxidant and/or anti-inflammatory properties, methods for their manufacture, and methods for their use, including for the treatment and/or prevention of disease.

I. DEFINITIONS

When used in the context of a chemical group: "hydrogen" means —H; "hydroxy" means —OH; "oxo" means =O; "carbonyl" means —C(=O)—; "carboxy" means —C(=O)OH (also written as —COOH or —CO_2H); "halo" means independently —F, —Cl, —Br or —I; "amino" means —NH_2; "hydroxyamino" means —NHOH; "nitro" means —NO_2; imino means =NH; "cyano" means —CN; "isocyanate" means —N=C=O; "azido" means —N_3; in a monovalent context "phosphate" means —OP(O)$(OH)_2$ or a deprotonated form thereof; in a divalent context "phosphate" means —OP(O)(OH)O— or a deprotonated form thereof; "mercapto" means —SH; and "thio" means =S; "sulfonyl" means —$S(O)_2$—; and "sulfinyl" means —S(O)—.

In the context of chemical formulas, the symbol "—" means a single bond, "=" means a double bond, and "≡" means triple bond. The symbol "----" represents an optional bond, which if present is either single or double. The symbol "" represents a single bond or a double bond. Thus, for example, the formula

includes

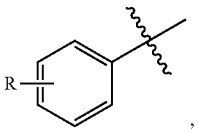


And it is understood that no one such ring atom forms part of more than one double bond. Furthermore, it is noted that the covalent bond symbol "—", when connecting one or two stereogenic atoms, does not indicate any preferred stereochemistry. Instead, it cover all stereoisomers as well as mixtures thereof. The symbol "", when drawn perpendicularly across a bond (e.g.,

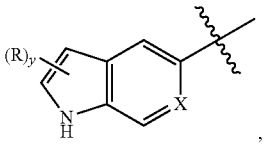
for methyl) indicates a point of attachment of the group. It is noted that the point of attachment is typically only identified in this manner for larger groups in order to assist the reader in unambiguously identifying a point of attachment. The symbol "◀" means a single bond where the group attached to the thick end of the wedge is "out of the page." The symbol "▮▮▮" means a single bond where the group attached to the thick end of the wedge is "into the page". The symbol "〰" means a single bond where the geometry around a double bond (e.g., either E or Z) is undefined. Both options, as well as combinations thereof are therefore intended. The bond orders described above are not limiting when one of the atoms connected by the bond is a metal atom (M). In such cases, it is understood that the actual bonding may comprise significant multiple bonding and/or ionic character. Therefore, unless indicated otherwise, the formulas M-C, M=C, M----C, and

each refers to a bond of any and type and order between a metal atom and a carbon atom. Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to that atom. A bold dot on a carbon atom indicates that the hydrogen attached to that carbon is oriented out of the plane of the paper.

When a group "R" is depicted as a "floating group" on a ring system, for example, in the formula:



then R may replace any hydrogen atom attached to any of the ring atoms, including a depicted, implied, or expressly defined hydrogen, so long as a stable structure is formed. When a group "R" is depicted as a "floating group" on a fused ring system, as for example in the formula:



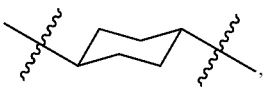
then R may replace any hydrogen attached to any of the ring atoms of either of the fused rings unless specified otherwise. Replaceable hydrogens include depicted hydrogens (e.g., the hydrogen attached to the nitrogen in the formula above), implied hydrogens (e.g., a hydrogen of the formula above that is not shown but understood to be present), expressly defined hydrogens, and optional hydrogens whose presence depends on the identity of a ring atom (e.g., a hydrogen attached to group X, when X equals —CH—), so long as a stable structure is formed. In the example depicted, R may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula above, the subscript letter "y" immediately following the group "R" enclosed in parentheses, represents a numeric variable. Unless specified otherwise, this variable can be 0, 1, 2, or any integer greater than 2, only limited by the maximum number of replaceable hydrogen atoms of the ring or ring system.

For the groups and classes below, the following parenthetical subscripts further define the group/class as follows: "(Cn)" defines the exact number (n) of carbon atoms in the group/class. "(C≤n)" defines the maximum number (n) of carbon atoms that can be in the group/class, with the minimum number as small as possible for the group in question, e.g., it is understood that the minimum number of carbon atoms in the group "alkenyl$_{(C\leq 8)}$" or the class "alkene$_{(C\leq 8)}$" is two. For example, "alkoxy$_{(C\leq 10)}$" designates those alkoxy groups having from 1 to 10 carbon atoms. (Cn–n') defines both the minimum (n) and maximum number (n') of carbon atoms in the group. Similarly, "alkyl$_{(C2\text{-}10)}$" designates those alkyl groups having from 2 to 10 carbon atoms.

The term "saturated" as used herein means the compound or group so modified has no carbon-carbon double and no carbon-carbon triple bonds, except as noted below. In the case of substituted versions of saturated groups, one or more carbon oxygen double bond or a carbon nitrogen double bond may be present. And when such a bond is present, then carbon-carbon double bonds that may occur as part of keto-enol tautomerism or imine/enamine tautomerism are not precluded.

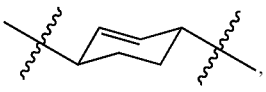
The term "aliphatic" when used without the "substituted" modifier signifies that the compound/group so modified is an acyclic or cyclic, but non-aromatic hydrocarbon compound or group. In aliphatic compounds/groups, the carbon atoms can be joined together in straight chains, branched chains, or non-aromatic rings (alicyclic). Aliphatic compounds/groups can be saturated, that is joined by single bonds (alkanes/alkyl), or unsaturated, with one or more double bonds (alkenes/alkenyl) or with one or more triple bonds (alkanes/alkenyl).

The term "alkyl" when used without the "substituted" modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, and no atoms other than carbon and hydrogen. Thus, as used herein cycloalkyl is a subset of alkyl, with the carbon atom that forms the point of attachment also being a member of one or more non-aromatic ring structures wherein the cycloalkyl group consists of no atoms other than carbon and hydrogen. As used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the ring or ring system. The groups —CH_3 (Me), —CH_2CH_3 (Et), —$CH_2CH_2CH_3$ (n-Pr or propyl), —$CH(CH_3)_2$ (i-Pr, ^{i}Pr or isopropyl), —$CH(CH_2)_2$ (cyclopropyl), —$CH_2CH_2CH_2CH_3$ (n-Bu), —$CH(CH_3)CH_2CH_3$ (sec-butyl), —$CH_2CH(CH_3)_2$ (isobutyl), —$C(CH_3)_3$ (tert-butyl, t-butyl, t-Bu or ^{t}Bu), —$CH_2C(CH_3)_3$ (neo-pentyl), cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexylmethyl are non-limiting examples of alkyl groups. The term "alkanediyl" when used without the "substituted" modifier refers to a divalent saturated aliphatic group, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, —CH_2-(methylene), —CH_2CH_2—, —$CH_2C(CH_3)_2CH_2$—, —$CH_2CH_2CH_2$—, and



are non-limiting examples of alkanediyl groups. The term "alkylidene" when used without the "substituted" modifier refers to the divalent group =CRR' in which R and R' are independently hydrogen, alkyl, or R' and R' are taken together to represent an alkanediyl having at least two carbon atoms. Non-limiting examples of alkylidene groups include: $=CH_2$, $=CH(CH_2CH_3)$, and $=C(CH_3)_2$. An "alkane" refers to the compound H—R, wherein R is alkyl as this term is defined above. When any of these terms is used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, $—NH_2$, $—NO_2$, $—CO_2H$, $—CO_2CH_3$, —CN, —SH, $—OCH_3$, $—OCH_2CH_3$, $—C(O)CH_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—N(CH_3)_2$, $—C(O)NH_2$, $—OC(O)CH_3$, or $—S(O)_2NH_2$. The following groups are non-limiting examples of substituted alkyl groups: $—CH_2OH$, $—CH_2Cl$, $—CF_3$, $—CH_2CN$, $—CH_2C(O)OH$, $—CH_2C(O)OCH_3$, $—CH_2C(O)NH_2$, $—CH_2C(O)CH_3$, $—CH_2OCH_3$, $—CH_2OC(O)CH_3$, $—CH_2NH_2$, $—CH_2N(CH_3)_2$, and $—CH_2CH_2Cl$. The term "haloalkyl" is a subset of substituted alkyl, in which one or more hydrogen atoms has been substituted with a halo group and no other atoms aside from carbon, hydrogen and halogen are present. The group, $—CH_2Cl$ is a non-limiting example of a haloalkyl. The term "fluoroalkyl" is a subset of substituted alkyl, in which one or more hydrogen has been substituted with a fluoro group and no other atoms aside from carbon, hydrogen and fluorine are present. The groups, $—CH_2F$, $—CF_3$, and $—CH_2CF_3$ are non-limiting examples of fluoroalkyl groups.

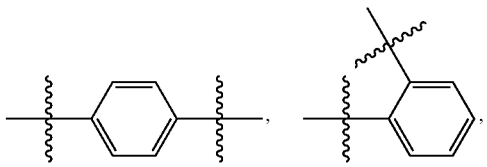
The term "alkenyl" when used without the "substituted" modifier refers to an monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one non-aromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of alkenyl groups include: $—CH=CH_2$ (vinyl), $—CH=CHCH_3$, $—CH=CHCH_2CH_3$, $—CH_2CH=CH_2$ (allyl), $—CH_2CH=CHCH_3$, and $—CH=CHCH=CH_2$. The term "alkenediyl" when used without the "substituted" modifier refers to a divalent unsaturated aliphatic group, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. The groups, —CH=CH—, $—CH=C(CH_3)CH_2—$, $—CH=CHCH_2—$, and



are non-limiting examples of alkenediyl groups. It is noted that while the alkenediyl group is aliphatic, once connected at both ends, this group is not precluded from forming part of an aromatic structure. The terms "alkene" or "olefin" are synonymous and refer to a compound having the formula H—R, wherein R is alkenyl as this term is defined above. A "terminal alkene" refers to an alkene having just one carbon-carbon double bond, wherein that bond forms a vinyl group at one end of the molecule. When any of these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, $—NH_2$, $—NO_2$, $—CO_2H$, $—CO_2CH_3$, —CN, —SH, $—OCH_3$, $—OCH_2CH_3$, $—C(O)CH_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—N(CH_3)_2$, $—C(O)NH_2$, $—OC(O)CH_3$, or $—S(O)_2NH_2$. The groups, —CH=CHF, —CH=CHCl and —CH=CHBr, are non-limiting examples of substituted alkenyl groups.

The term "alkynyl" when used without the "substituted" modifier refers to an monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. As used herein, the term alkynyl does not preclude the presence of one or more non-aromatic carbon-carbon double bonds. The groups, —C≡CH, $—C≡CCH_3$, and $—CH_2C≡CCH_3$, are non-limiting examples of alkynyl groups. An "alkyne" refers to the compound H—R, wherein R is alkynyl. When any of these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, $—NH_2$, $—NO_2$, $—CO_2H$, $—CO_2CH_3$, —CN, —SH, $—OCH_3$, $—OCH_2CH_3$, $—C(O)CH_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—N(CH_3)_2$, $—C(O)NH_2$, $—OC(O)CH_3$, or $—S(O)_2NH_2$.

The term "aryl" when used without the "substituted" modifier refers to a monovalent unsaturated aromatic group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a one or more six-membered aromatic ring structure, wherein the ring atoms are all carbon, and wherein the group consists of no atoms other than carbon and hydrogen. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, $—C_6H_4—CH_2CH_3$ (ethylphenyl), naphthyl, and a monovalent group derived from biphenyl. The term "arenediyl" when used without the "substituted" modifier refers to a divalent aromatic group with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. As used herein, the term does not preclude the presence of one or more alkyl, aryl or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. If more than one ring is present, the rings may be fused or unfused. Unfused rings may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). Non-limiting examples of arenediyl groups include:



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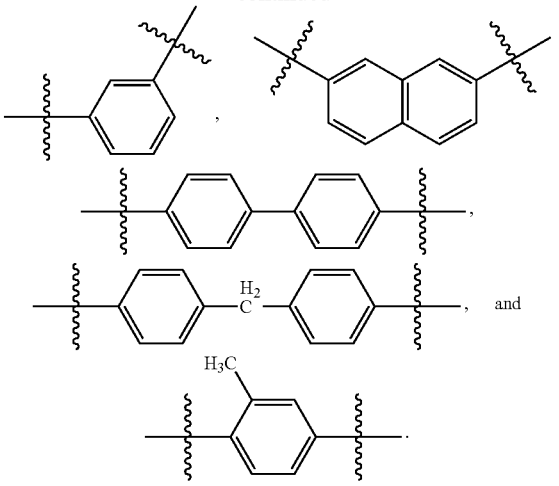
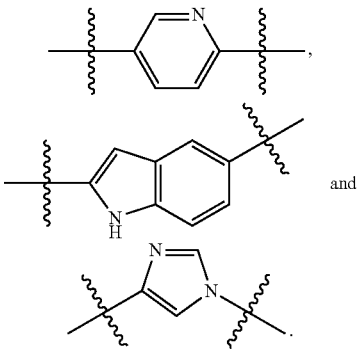


An "arene" refers to the compound H—R, wherein R is aryl as that term is defined above. Benzene and toluene are non-limiting examples of arenes. When any of these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH_2, —NO_2, —CO_2H, —CO_2CH_3, —CN, —SH, —OCH_3, —OCH_2CH_3, —$C(O)CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, —$C(O)NH_2$, —$OC(O)CH_3$, or —$S(O)_2NH_2$.

The term "aralkyl" when used without the "substituted" modifier refers to the monovalent group -alkanediyl-aryl, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: phenylmethyl (benzyl, Bn) and 2-phenyl-ethyl. When the term aralkyl is used with the "substituted" modifier one or more hydrogen atom from the alkanediyl and/or the aryl group has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH_2, —NO_2, —CO_2H, —CO_2CH_3, —CN, —SH, —OCH_3, —OCH_2CH_3, —$C(O)CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, —$C(O)NH_2$, —$OC(O)CH_3$, or —$S(O)_2NH_2$. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, and 2-chloro-2-phenyl-eth-1-yl.

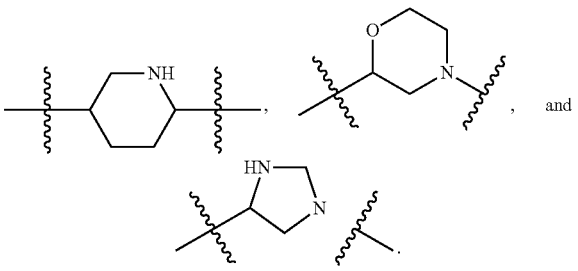
The term "heteroaryl" when used without the "substituted" modifier refers to a monovalent aromatic group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more aromatic ring structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the heteroaryl group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl, aryl, and/or aralkyl groups (carbon number limitation permitting) attached to the aromatic ring or aromatic ring system. Non-limiting examples of heteroaryl groups include furanyl, imidazolyl, indolyl, indazolyl (Im), isoxazolyl, methylpyridinyl, oxazolyl, phenylpyridinyl, pyridinyl, pyrrolyl, pyrimidinyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, triazinyl, tetrazolyl, thiazolyl, thienyl, and triazolyl. The term "N-heteroaryl" refers to a heteroaryl group with a nitrogen atom as the point of attachment. The term "heteroarenediyl" when used without the "substituted" modifier refers to an divalent aromatic group, with two aromatic carbon atoms, two aromatic nitrogen atoms, or one aromatic carbon atom and one aromatic nitrogen atom as the two points of attachment, said atoms forming part of one or more aromatic ring structure(s) wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. If more than one ring is present, the rings may be fused or unfused. Unfused rings may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). As used herein, the term does not preclude the presence of one or more alkyl, aryl, and/or aralkyl groups (carbon number limitation permitting) attached to the aromatic ring or aromatic ring system. Non-limiting examples of heteroarenediyl groups include:



A "heteroarene" refers to the compound H—R, wherein R is heteroaryl. Pyridine and quinoline are non-limiting examples of heteroarenes. When these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH_2, —NO_2, —CO_2H, —CO_2CH_3, —CN, —SH, —OCH_3, —OCH_2CH_3, —$C(O)CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, —$C(O)NH_2$, —$OC(O)CH_3$, or —$S(O)_2NH_2$.

The term "heterocycloalkyl" when used without the "substituted" modifier refers to a monovalent non-aromatic group with a carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more non-aromatic ring structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the heterocycloalkyl group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and sulfur. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the ring or ring system. Also, the term does not preclude the presence of one or more double bonds in the ring or ring system, provided that the resulting group remains non-aromatic. Non-limiting examples of heterocycloalkyl groups include aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, pyranyl, oxiranyl, and oxetanyl. The term "N-heterocycloalkyl" refers to a heterocycloalkyl group with a nitrogen atom as the point of attachment. The term "heterocycloalkanediyl" when used without the "substituted" modifier refers to an divalent cyclic group, with two carbon atoms, two nitrogen atoms, or one carbon atom and one nitrogen atom as the two points of attachment, said atoms forming part of one or more ring structure(s) wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and

sulfur. If more than one ring is present, the rings may be fused or unfused. Unfused rings may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). As used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the ring or ring system. Also, the term does not preclude the presence of one or more double bonds in the ring or ring system, provided that the resulting group remains non-aromatic. Non-limiting examples of heterocycloalkanediyl groups include:



and

When these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH_2, —NO_2, —CO_2H, —CO_2CH_3, —CN, —SH, —OCH_3, —OCH_2CH_3, —C(O)CH_3, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, C(O)NH_2, $OC(O)CH_3$, $S(O)_2NH_2$, or —$C(O)OC(CH_3)_3$ (tert-butyloxycarbonyl, BOC).

The term "acyl" when used without the "substituted" modifier refers to the group —C(O)R, in which R is a hydrogen, alkyl, aryl, aralkyl or heteroaryl, as those terms are defined above. The groups, —CHO, —$C(O)CH_3$ (acetyl, Ac), —$C(O)CH_2CH_3$, —$C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH(CH_2)_2$, $C(O)C_6H_5$, $C(O)C_6H_4CH_3$, —C(O)$CH_2C_6H_5$, —C(O)(imidazolyl) are non-limiting examples of acyl groups. A "thioacyl" is defined in an analogous manner, except that the oxygen atom of the group —C(O)R has been replaced with a sulfur atom, —C(S)R. The term "aldehyde" corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with a —CHO group. When any of these terms are used with the "substituted" modifier one or more hydrogen atom (including a hydrogen atom directly attached the carbonyl or thiocarbonyl group, if any) has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH_2, —NO_2, —CO_2H, —CO_2CH_3, —CN, —SH, —OCH_3, —OCH_2CH_3, —$C(O)CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, —$C(O)NH_2$, —OC(O)CH_3, or —$S(O)_2NH_2$. The groups, —$C(O)CH_2CF_3$, —CO_2H (carboxyl), —CO_2CH_3 (methylcarboxyl), —$CO_2CH_2CH_3$, —$C(O)NH_2$ (carbamoyl), and —CON$(CH_3)_2$, are non-limiting examples of substituted acyl groups.

The term "alkoxy" when used without the "substituted" modifier refers to the group —OR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkoxy groups include: —OCH_3 (methoxy), —OCH_2CH_3 (ethoxy), —$OCH_2CH_2CH_3$, —$OCH(CH_3)_2$ (isopropoxy), —$O(CH_3)_3$ (tert-butoxy), —$OCH(CH_2)_2$, —O-cyclopentyl, and —O-cyclohexyl. The terms "alkenyloxy", "alkynyloxy", "aryloxy", "aralkoxy", "heteroaryloxy", "heterocycloalkoxy", and "acyloxy", when used without the "substituted" modifier, refers to groups, defined as —OR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, and acyl, respectively. The term "alkoxydiyl" refers to the divalent group —O-alkanediyl-, —O-alkanediyl—O—, or -alkanediyl—O-alkanediyl-. The term "alkylthio" and "acylthio" when used without the "substituted" modifier refers to the group —SR, in which R is an alkyl and acyl, respectively. The term "alcohol" corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with a hydroxy group. The term "ether" corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with an alkoxy group. When any of these terms is used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH_2, —NO_2, —CO_2H, —CO_2CH_3, —CN, —SH, —OCH_3, —OCH_2CH_3, —$C(O)CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, —$C(O)NH_2$, —OC(O)CH_3, or —$S(O)_2NH_2$.

The term "alkylamino" when used without the "substituted" modifier refers to the group —NHR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylamino groups include: —$NHCH_3$ and —$NHCH_2CH_3$. The term "dialkylamino" when used without the "substituted" modifier refers to the group —NRR', in which R and R' can be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl. Non-limiting examples of dialkylamino groups include: —$N(CH_3)_2$, —$N(CH_3)(CH_2CH_3)$, and N-pyrrolidinyl. The terms "alkoxyamino", "alkenylamino", "alkynylamino", "arylamino", "aralkylamino", "heteroarylamino", "heterocycloalkylamino" and "alkylsulfonylamino" when used without the "substituted" modifier, refers to groups, defined as —NHR, in which R is alkoxy, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, and alkylsulfonyl, respectively. A non-limiting example of an arylamino group is —NHC_6H_5. The term "amido" (acylamino), when used without the "substituted" modifier, refers to the group —NHR, in which R is acyl, as that term is defined above. A non-limiting example of an amido group is —$NHC(O)CH_3$. The term "alkylimino" when used without the "substituted" modifier refers to the divalent group =NR, in which R is an alkyl, as that term is defined above. The term "alkylaminodiyl" refers to the divalent group —NH-alkanediyl-, —NH-alkanediyl—NH—, or -alkanediyl—NH-alkanediyl-. When any of these terms is used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH_2, —NO_2, —CO_2H, —CO_2CH_3, —CN, —SH, —OCH_3, —OCH_2CH_3, —$C(O)CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, —$C(O)NH_2$, —OC(O)CH_3, or —$S(O)_2NH_2$. The groups —$NHC(O)OCH_3$ and —$NHC(O)NHCH_3$ are non-limiting examples of substituted amido groups.

The terms "alkylsulfonyl" and "alkylsulfinyl" when used without the "substituted" modifier refers to the groups —$S(O)_2R$ and —S(O)R, respectively, in which R is an alkyl, as that term is defined above. The terms "alkenylsulfonyl", "alkynylsulfonyl", "arylsulfonyl", "aralkylsulfonyl", "heteroarylsulfonyl", and "heterocycloalkylsulfonyl" are defined in an analogous manner. When any of these terms is used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH_2, —NO_2, —CO_2H, —CO_2CH_3, —CN, —SH, —OCH_3, —OCH_2CH_3, —$C(O)CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, —$C(O)NH_2$, —OC(O)CH_3, or —$S(O)_2NH_2$.

The term "alkylphosphate" when used without the "substituted" modifier refers to the group —OP(O)(OH)(OR), in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylphosphate groups include: —OP(O)(OH)(OMe) and —OP(O)(OH)(OEt). The term "dialky-

lphosphate" when used without the "substituted" modifier refers to the group —OP(O)(OR)(OR'), in which R and R' can be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl. Non-limiting examples of dialkylphosphate groups include: —OP(O)(OMe)$_2$, —OP(O)(OEt)(OMe) and —OP(O)(OEt)$_2$. When any of these terms is used with the "substituted" modifier one or more hydrogen atom has been independently replaced by —OH, —F, —Cl, —Br, —I, —NH$_2$, —NO$_2$, —CO$_2$H, —CO$_2$CH$_3$, —CN, —SH, —OCH$_3$, —OCH$_2$CH$_3$, —C(O)CH$_3$, —NHCH$_3$, —NHCH$_2$CH$_3$, —N(CH$_3$)$_2$, —C(O)NH$_2$, —OC(O)CH$_3$, Or —S(O)$_2$NH$_2$.

The use of the word "a" or "an," when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

As used herein, a "chiral auxiliary" refers to a removable chiral group that is capable of influencing the stereoselectivity of a reaction. Persons of skill in the art are familiar with such compounds, and many are commercially available.

The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

The term "effective," as that term is used in the specification and/or claims, means adequate to accomplish a desired, expected, or intended result. "Effective amount," "Therapeutically effective amount" or "pharmaceutically effective amount" when used in the context of treating a patient or subject with a compound means that amount of the compound which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

As used herein, the term "IC$_{50}$" refers to an inhibitory dose which is 50% of the maximum response obtained. This quantitative measure indicates how much of a particular drug or other substance (inhibitor) is needed to inhibit a given biological, biochemical or chemical process (or component of a process, i.e. an enzyme, cell, cell receptor or microorganism) by half.

An "isomer" of a first compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but where the configuration of those atoms in three dimensions differs.

As used herein, the term "patient" or "subject" refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

As generally used herein "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues, organs, and/or bodily fluids of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salts" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo [2.2.2] oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, o-(4-hydroxybenzoyl)benzoic acid, oxalic acid, p-chlorobenzenesulfonic acid, phenyl-substituted alkanoic acids, propionic acid, p-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (P. H. Stahl & C. G. Wermuth eds., Verlag Helvetica Chimica Acta, 2002).

The term "pharmaceutically acceptable carrier," as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

"Prevention" or "preventing" includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

"Prodrug" means a compound that is convertible in vivo metabolically into an inhibitor according to the present invention. The prodrug itself may or may not also have activity with respect to a given target protein. For example, a compound comprising a hydroxy group may be administered as an ester that is converted by hydrolysis in vivo to the hydroxy compound. Suitable esters that may be converted in vivo into hydroxy compounds include acetates, citrates, lactates, phosphates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoate, gentisates, isethionates, di-p-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates, quinates, esters of amino acids, and the like. Similarly,

a compound comprising an amine group may be administered as an amide that is converted by hydrolysis in vivo to the amine compound.

A "stereoisomer" or "optical isomer" is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. "Enantiomers" are stereoisomers of a given compound that are mirror images of each other, like left and right hands. "Diastereomers" are stereoisomers of a given compound that are not enantiomers. Chiral molecules contain a chiral center, also referred to as a stereocenter or stereogenic center, which is any point, though not necessarily an atom, in a molecule bearing groups such that an interchanging of any two groups leads to a stereoisomer. In organic compounds, the chiral center is typically a carbon, phosphorus or sulfur atom, though it is also possible for other atoms to be stereocenters in organic and inorganic compounds. A molecule can have multiple stereocenters, giving it many stereoisomers. In compounds whose stereoisomerism is due to tetrahedral stereogenic centers (e.g., tetrahedral carbon), the total number of hypothetically possible stereoisomers will not exceed 2n, where n is the number of tetrahedral stereocenters. Molecules with symmetry frequently have fewer than the maximum possible number of stereoisomers. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Alternatively, a mixture of enantiomers can be enantiomerically enriched so that one enantiomer is present in an amount greater than 50%. Typically, enantiomers and/or diastereomers can be resolved or separated using techniques known in the art. It is contemplated that that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality can be present in its R form, S form, or as a mixture of the R and S forms, including racemic and non-racemic mixtures. As used herein, the phrase "substantially free from other stereoisomers" means that the composition contains ≤15%, more preferably ≤10%, even more preferably ≤5%, or most preferably ≤1% of another stereoisomer(s).

"Treatment" or "treating" includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (e.g., arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease (e.g., reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

Other abbreviations used herein are as follows: DMSO, dimethyl sulfoxide; DMF, dimethylformamide; MeOH, methanol; EtOH, ethanol; THF, tetrahydrofuran; MTBE, methyl tert-butyl ether; DCM, dichloromethane; t-BuOH, tert-butanol; EtOAc, ethyl acetate; AcOH, acetic acid; TFA, trifluoroacetic acid; p-TsOH or PTSA, p-toluenesulfonic acid; Et_3N or TEA, triethylamine; DIPEA or DIEA, diisopropylethylamine; DMAP, dimethylaminopyridine; Ac_2O, acetic anhydride; TFAA, trifluoroacetic anhydride; 4 Å MS, 4 angstrom molecular sieves; NMO, N-methylmorpholine N-oxide; TPAP, tetrapropylammonium perruthenate; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin; HC(O)OEt, ethyl formate; TBSCl, tertbutyldimethylsilyl chloride; Et_2NSF_3, diethylaminosulfur trifluoride; NaOAc, sodium acetate; MOMCl, methyl chloromethyl ether; TBAF, tetrabutylammonium fluoride; n-BuLi, n-butyllithium; iPrLi, isopropyllithium; $TMSCHN_2$, (trimethylsilyl)diazomethane solution; h or hr, hour(s); RBF, round bottom flask; SM, starting material; NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; FBS, fetal bovine serum; IFNγ or IFN-γ, interferon-γ; TNFα or TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; HO-1, inducible heme oxygenase.

The above definitions supersede any conflicting definition in any of the reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms used are believed to describe the invention in terms such that one of ordinary skill can appreciate the scope and practice the present invention.

II. COMPOUNDS AND SYNTHETIC METHODS

The compounds provided by the present disclosure are shown above in the summary of the invention section and in the claims below. They may be made using the methods outlined in the Examples section. These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (2007), which is incorporated by reference herein.

Compounds of the invention may contain one or more asymmetrically-substituted carbon or nitrogen atoms, and may be isolated in optically active or racemic form. Thus, all chiral, diastereomeric, racemic form, epimeric form, and all geometric isomeric forms of a chemical formula are intended, unless the specific stereochemistry or isomeric form is specifically indicated. Compounds may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. In some embodiments, a single diastereomer is obtained. The chiral centers of the compounds of the present invention can have the S or the R configuration.

Chemical formulas used to represent compounds of the invention will typically only show one of possibly several different tautomers. For example, many types of ketone groups are known to exist in equilibrium with corresponding enol groups. Similarly, many types of imine groups exist in equilibrium with enamine groups. Regardless of which tautomer is depicted for a given compound, and regardless of which one is most prevalent, all tautomers of a given chemical formula are intended.

Atoms making up the compounds of the present invention are intended to include all isotopic forms of such atoms. Compounds of the present invention include those with one or more atoms that have been isotopically modified or enriched, in particular those with pharmaceutically acceptable isotopes or those useful for pharmaceutically research. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium, and isotopes of carbon include ^{13}C and ^{14}C. Similarly, it is contemplated that one or more carbon atom(s) of a compound of the present invention may be replaced by a silicon atom(s). Furthermore, it is contemplated that one or more oxygen atom(s) of a compound of the present invention may be replaced by a sulfur or selenium atom(s).

Compounds of the present invention may also exist in prodrug form. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.), the compounds employed in some methods of the invention may, if desired, be delivered in prodrug form. Thus, the invention contemplates prodrugs of compounds of the present invention as well

as methods of delivering prodrugs. Prodrugs of the compounds employed in the invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a subject, cleaves to form a hydroxy, amino, or carboxylic acid, respectively.

It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (2002), which is incorporated herein by reference.

It should be further recognized that the compounds of the present invention include those that have been further modified to comprise substituents that are convertible to hydrogen in vivo. This includes those groups that may be convertible to a hydrogen atom by enzymological or chemical means including, but not limited to, hydrolysis and hydrogenolysis. Examples include hydrolyzable groups, such as acyl groups, groups having an oxycarbonyl group, amino acid residues, peptide residues, o-nitrophenylsulfenyl, trimethylsilyl, tetrahydropyranyl, diphenylphosphinyl, and the like. Examples of acyl groups include formyl, acetyl, trifluoroacetyl, and the like. Examples of groups having an oxycarbonyl group include ethoxycarbonyl, tert-butoxycarbonyl (—C(O)OC$(CH_3)_3$, Boc), benzyloxycarbonyl, p-methoxy-benzyloxycarbonyl, vinyloxycarbonyl, β-(p-toluenesulfonyl)ethoxycarbonyl, and the like. Suitable amino acid residues include, but are not limited to, residues of Gly (glycine), Ala (alanine), Arg (arginine), Asn (asparagine), Asp (aspartic acid), Cys (cysteine), Glu (glutamic acid), His (histidine), Ile (isoleucine), Leu (leucine), Lys (lysine), Met (methionine), Phe (phenylalanine), Pro (proline), Ser (serine), Thr (threonine), Trp (tryptophan), Tyr (tyrosine), Val (valine), Nva (norvaline), Hse (homoserine), 4-Hyp (4-hydroxyproline), 5-Hyl (5-hydroxylysine), Orn (ornithine) and β-Ala. Examples of suitable amino acid residues also include amino acid residues that are protected with a protecting group. Examples of suitable protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethoxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), tert-butoxycarbonyl groups (—C(O)OC$(CH_3)_3$, Boc), and the like. Suitable peptide residues include peptide residues comprising two to five amino acid residues. The residues of these amino acids or peptides can be present in stereochemical configurations of the D-form, the L-form or mixtures thereof. In addition, the amino acid or peptide residue may have an asymmetric carbon atom. Examples of suitable amino acid residues having an asymmetric carbon atom include residues of Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr and Tyr. Peptide residues having an asymmetric carbon atom include peptide residues having one or more constituent amino acid residues having an asymmetric carbon atom. Examples of suitable amino acid protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethoxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), tert-butoxycarbonyl groups (—C(O)OC$(CH_3)_3$), and the like. Other examples of substituents "convertible to hydrogen in vivo" include reductively eliminable hydrogenolyzable groups. Examples of suitable reductively eliminable hydrogenolyzable groups include, but are not limited to, arylsulfonyl groups (such as o-toluenesulfonyl); methyl groups substituted with phenyl or benzyloxy (such as benzyl, trityl and benzyloxymethyl); arylmethoxycarbonyl groups (such as benzyloxycarbonyl and o-methoxy-benzyloxycarbonyl); and haloethoxycarbonyl groups (such as β,β,β--trichloroethoxycarbonyl and β-iodoethoxycarbonyl).

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g., higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the indications stated herein or otherwise.

III. BIOLOGICAL ACTIVITY

Assay results for the suppression of IFNγ-induced NO production are shown for several of the compounds of the present invention in Table 1 below. In the right-hand column of this table under the RAW264.7 heading, the results are compared to those of bardoxolone methyl (RTA 402, CDDO-Me). Details regarding this assay are provided in the Examples section below.

TABLE 1

Suppression of IFNγ-Induced NO Production.

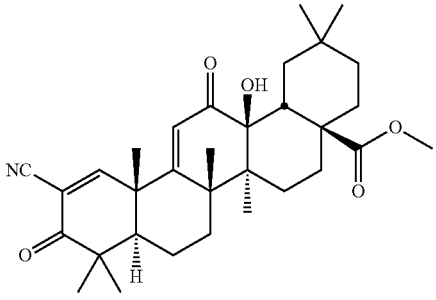
			RAW264.7	
Compound No.	Molecular Structure	MW	NO IC_{50} (nM)	Relative NO IC_{50}
TX63421		521.70	2.3	0.8

TABLE 1-continued

Suppression of IFNγ-Induced NO Production.

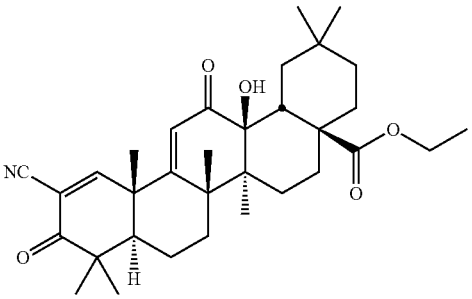
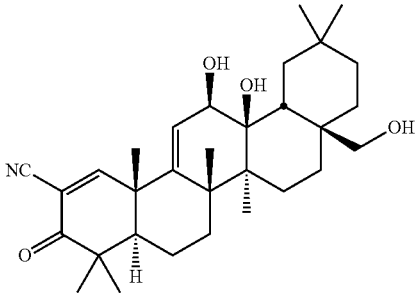
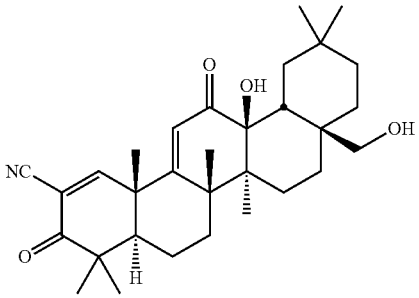
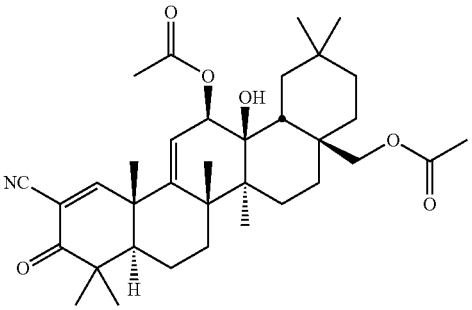
Compound No.	Molecular Structure	MW	RAW264.7 NO IC_{50} (nM)	RAW264.7 Relative NO IC_{50}
TX63469		535.72	2.2	1.2
TX63489		495.70	61	14
TX63490		493.70	1.5	1.1
TX63498		579.77	24	15

TABLE 1-continued

Suppression of IFNγ-Induced NO Production.

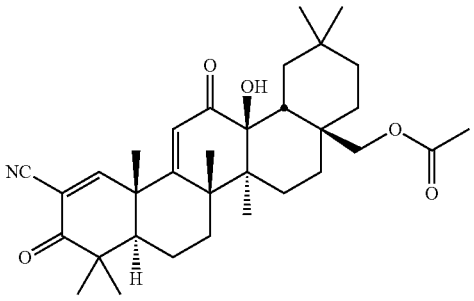
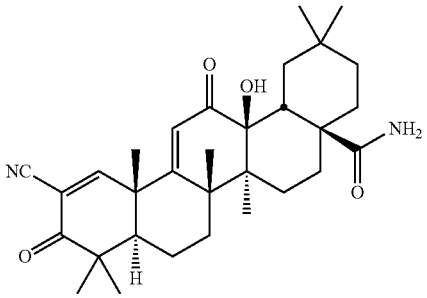
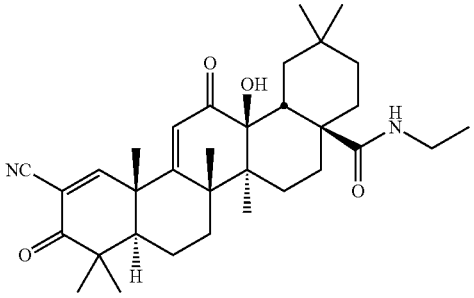
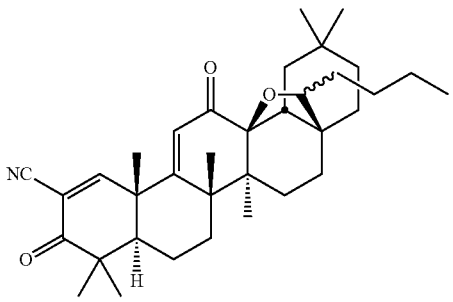
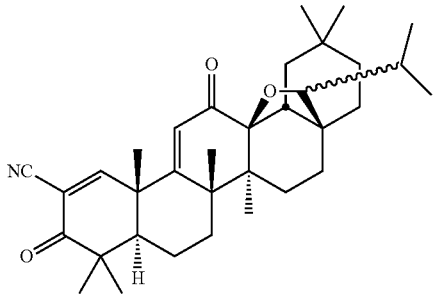
Compound No.	Molecular Structure	MW	RAW264.7 NO IC_{50} (nM)	RAW264.7 Relative NO IC_{50}
TX63499		535.72	2.1	1.3
TX63530		506.68	1.4	0.8
TX63536		534.74	5.6	2.7
TX63481		531.79	37	19.5
TX63484	 single diastereomer (B)	531.79	37	19.5

TABLE 1-continued

Suppression of IFNγ-Induced NO Production.

Compound No.	Molecular Structure	MW	RAW264.7 NO IC_{50} (nM)	RAW264.7 Relative NO IC_{50}
TX63496	 single diastereomer (A)	531.79	37	19.5

IV. DISEASES ASSOCIATED WITH INFLAMMATION AND/OR OXIDATIVE STRESS

Inflammation is a biological process that provides resistance to infectious or parasitic organisms and the repair of damaged tissue. Inflammation is commonly characterized by localized vasodilation, redness, swelling, and pain, the recruitment of leukocytes to the site of infection or injury, production of inflammatory cytokines such as TNF-α and IL-1, and production of reactive oxygen or nitrogen species such as hydrogen peroxide, superoxide and peroxynitrite. In later stages of inflammation, tissue remodeling, angiogenesis, and scar formation (fibrosis) may occur as part of the wound healing process. Under normal circumstances, the inflammatory response is regulated and temporary and is resolved in an orchestrated fashion once the infection or injury has been dealt with adequately. However, acute inflammation can become excessive and life-threatening if regulatory mechanisms fail. Alternatively, inflammation can become chronic and cause cumulative tissue damage or systemic complications. Based at least on the evidence presented above, the compounds of this invention may be used in the treatment or prevention of inflammation or diseases associated with inflammation.

Many serious and intractable human diseases involve dysregulation of inflammatory processes, including diseases such as cancer, atherosclerosis, and diabetes, which were not traditionally viewed as inflammatory conditions. In the case of cancer, the inflammatory processes are associated with tumor formation, progression, metastasis, and resistance to therapy. Atherosclerosis, long viewed as a disorder of lipid metabolism, is now understood to be primarily an inflammatory condition, with activated macrophages playing an important role in the formation and eventual rupture of atherosclerotic plaques. Activation of inflammatory signaling pathways has also been shown to play a role in the development of insulin resistance, as well as in the peripheral tissue damage associated with diabetic hyperglycemia. Excessive production of reactive oxygen species and reactive nitrogen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite is a hallmark of inflammatory conditions. Evidence of dysregulated peroxynitrite production has been reported in a wide variety of diseases (Szabo et al., 2007; Schulz et al., 2008; Forstermann, 2006; Pall, 2007).

Autoimmune diseases such as rheumatoid arthritis, lupus, psoriasis, and multiple sclerosis involve inappropriate and chronic activation of inflammatory processes in affected tissues, arising from dysfunction of self vs. non-self recognition and response mechanisms in the immune system. In neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, neural damage is correlated with activation of microglia and elevated levels of pro-inflammatory proteins such as inducible nitric oxide synthase (iNOS). Chronic organ failure such as renal failure, heart failure, liver failure, and chronic obstructive pulmonary disease is closely associated with the presence of chronic oxidative stress and inflammation, leading to the development of fibrosis and eventual loss of organ function. Oxidative stress in vascular endothelial cells, which line major and minor blood vessels, can lead to endothelial dysfunction and is believed to be an important contributing factor in the development of systemic cardiovascular disease, complications of diabetes, chronic kidney disease and other forms of organ failure, and a number of other aging-related diseases including degenerative diseases of the central nervous system and the retina.

Many other disorders involve oxidative stress and inflammation in affected tissues, including inflammatory bowel disease; inflammatory skin diseases; mucositis related to radiation therapy and chemotherapy; eye diseases such as uveitis, glaucoma, macular degeneration, and various forms of retinopathy; transplant failure and rejection; ischemia-reperfusion injury; chronic pain; degenerative conditions of the bones and joints including osteoarthritis and osteoporosis; asthma and cystic fibrosis; seizure disorders; and neuropsychiatric conditions including schizophrenia, depression, bipolar disorder, post-traumatic stress disorder, attention deficit disorders, autism-spectrum disorders, and eating disorders such as anorexia nervosa. Dysregulation of inflammatory signaling pathways is believed to be a major factor in the pathology of muscle wasting diseases including muscular dystrophy and various forms of cachexia.

A variety of life-threatening acute disorders also involve dysregulated inflammatory signaling, including acute organ failure involving the pancreas, kidneys, liver, or lungs, myocardial infarction or acute coronary syndrome, stroke, septic shock, trauma, severe burns, and anaphylaxis.

Many complications of infectious diseases also involve dysregulation of inflammatory responses. Although an

inflammatory response can kill invading pathogens, an excessive inflammatory response can also be quite destructive and in some cases can be a primary source of damage in infected tissues. Furthermore, an excessive inflammatory response can also lead to systemic complications due to overproduction of inflammatory cytokines such as TNF-α and IL-1. This is believed to be a factor in mortality arising from severe influenza, severe acute respiratory syndrome, and sepsis.

The aberrant or excessive expression of either iNOS or cyclooxygenase-2 (COX-2) has been implicated in the pathogenesis of many disease processes. For example, it is clear that NO is a potent mutagen (Tamir and Tannebaum, 1996), and that nitric oxide can also activate COX-2 (Salvemini et al., 1994). Furthermore, there is a marked increase in iNOS in rat colon tumors induced by the carcinogen, azoxymethane (Takahashi et al., 1997). A series of synthetic triterpenoid analogs of oleanolic acid have been shown to be powerful inhibitors of cellular inflammatory processes, such as the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda et al. (2000a); Honda et al. (2000b), and Honda et al. (2002), which are all incorporated herein by reference.

In one aspect, compounds disclosed herein are characterized by their ability to inhibit the production of nitric oxide in macrophage-derived RAW 264.7 cells induced by exposure to γ-interferon. They are further characterized by their ability to induce the expression of antioxidant proteins such as NQ01 and reduce the expression of pro-inflammatory proteins such as COX-2 and inducible nitric oxide synthase (iNOS). These properties are relevant to the treatment of a wide array of diseases and disorders involving oxidative stress and dysregulation of inflammatory processes including cancer, complications from localized or total-body exposure to ionizing radiation, mucositis resulting from radiation therapy or chemotherapy, autoimmune diseases, cardiovascular diseases including atherosclerosis, ischemia-reperfusion injury, acute and chronic organ failure including renal failure and heart failure, respiratory diseases, diabetes and complications of diabetes, severe allergies, transplant rejection, graft-versus-host disease, neurodegenerative diseases, diseases of the eye and retina, acute and chronic pain, degenerative bone diseases including osteoarthritis and osteoporosis, inflammatory bowel diseases, dermatitis and other skin diseases, sepsis, burns, seizure disorders, and neuropsychiatric disorders.

Without being bound by theory, the activation of the anti-oxidant/anti-inflammatory Keap1/Nrf2/ARE pathway is believed to be implicated in both the anti-inflammatory and anti-carcinogenic properties of the compounds disclosed herein.

In another aspect, compounds disclosed herein may be used for treating a subject having a condition caused by elevated levels of oxidative stress in one or more tissues. Oxidative stress results from abnormally high or prolonged levels of reactive oxygen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite (formed by the reaction of nitric oxide and superoxide). The oxidative stress may be accompanied by either acute or chronic inflammation. The oxidative stress may be caused by mitochondrial dysfunction, by activation of immune cells such as macrophages and neutrophils, by acute exposure to an external agent such as ionizing radiation or a cytotoxic chemotherapy agent (e.g., doxorubicin), by trauma or other acute tissue injury, by ischemia/reperfusion, by poor circulation or anemia, by localized or systemic hypoxia or hyperoxia, by elevated levels of inflammatory cytokines and other inflammation-related proteins, and/or by other abnormal physiological states such as hyperglycemia or hypoglycemia.

In animal models of many such conditions, stimulating expression of inducible heme oxygenase (HO-1), a target gene of the Nrf2 pathway, has been shown to have a significant therapeutic effect including models of myocardial infarction, renal failure, transplant failure and rejection, stroke, cardiovascular disease, and autoimmune disease (e.g., Sacerdoti et al., 2005; Abraham & Kappas, 2005; Bach, 2006; Araujo et al., 2003; Liu et al., 2006; Ishikawa et al., 2001; Kruger et al., 2006; Satoh et al., 2006; Zhou et al., 2005; Morse and Choi, 2005; Morse and Choi, 2002). This enzyme breaks free heme down into iron, carbon monoxide (CO), and biliverdin (which is subsequently converted to the potent antioxidant molecule, bilirubin).

In another aspect, compounds of this invention may be used in preventing or treating tissue damage or organ failure, acute and chronic, resulting from oxidative stress exacerbated by inflammation. Examples of diseases that fall in this category include: heart failure, liver failure, transplant failure and rejection, renal failure, pancreatitis, fibrotic lung diseases (cystic fibrosis, COPD, and idiopathic pulmonary fibrosis, among others), diabetes (including complications), atherosclerosis, ischemia-reperfusion injury, glaucoma, stroke, autoimmune disease, autism, macular degeneration, and muscular dystrophy. For example, in the case of autism, studies suggest that increased oxidative stress in the central nervous system may contribute to the development of the disease (Chauhan and Chauhan, 2006).

Evidence also links oxidative stress and inflammation to the development and pathology of many other disorders of the central nervous system, including psychiatric disorders such as psychosis, major depression, and bipolar disorder; seizure disorders such as epilepsy; pain and sensory syndromes such as migraine, neuropathic pain or tinnitus; and behavioral syndromes such as the attention deficit disorders. See, e.g., Dickerson et al., 2007; Hanson et al., 2005; Kendall-Tackett, 2007; Lencz et al., 2007; Dudhgaonkar et al., 2006; Lee et al., 2007; Morris et al., 2002; Ruster et al., 2005; McIver et al., 2005; Sarchielli et al., 2006; Kawakami et al., 2006; Ross et al., 2003, which are all incorporated by reference herein. For example, elevated levels of inflammatory cytokines, including TNF, interferon-γ, and IL-6, are associated with major mental illness (Dickerson et al., 2007). Microglial activation has also been linked to major mental illness. Therefore, downregulating inflammatory cytokines and inhibiting excessive activation of microglia could be beneficial in patients with schizophrenia, major depression, bipolar disorder, autism-spectrum disorders, and other neuropsychiatric disorders.

Accordingly, in pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation, treatment may comprise administering to a subject a therapeutically effective amount of a compound of this invention, such as those described above or throughout this specification. Treatment may be administered preventively, in advance of a predictable state of oxidative stress (e.g., organ transplantation or the administration of radiation therapy to a cancer patient), or it may be administered therapeutically in settings involving established oxidative stress and inflammation.

The compounds disclosed herein may be generally applied to the treatment of inflammatory conditions, such as sepsis, dermatitis, autoimmune disease and osteoarthritis. In one aspect, the compounds of this invention may be used to treat inflammatory pain and/or neuropathic pain, for example, by inducing Nrf2 and/or inhibiting NF-κB.

In some embodiments, the compounds disclosed herein may be used in the treatment and prevention of diseases such as cancer, inflammation, Alzheimer's disease, Parkinson's

disease, multiple sclerosis, autism, amyotrophic lateral sclerosis, Huntington's disease, autoimmune diseases such as rheumatoid arthritis, lupus, Crohn's disease and psoriasis, inflammatory bowel disease, all other diseases whose pathogenesis is believed to involve excessive production of either nitric oxide or prostaglandins, and pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation.

Another aspect of inflammation is the production of inflammatory prostaglandins such as prostaglandin E. These molecules promote vasodilation, plasma extravasation, localized pain, elevated temperature, and other symptoms of inflammation. The inducible form of the enzyme COX-2 is associated with their production, and high levels of COX-2 are found in inflamed tissues. Consequently, inhibition of COX-2 may relieve many symptoms of inflammation and a number of important anti-inflammatory drugs (e.g., ibuprofen and celecoxib) act by inhibiting COX-2 activity. Recent research, however, has demonstrated that a class of cyclopentenone prostaglandins (cyPGs) (e.g., 15-deoxy prostaglandin J2, a.k.a. PGJ2) plays a role in stimulating the orchestrated resolution of inflammation (e.g., Rajakariar et al., 2007). COX-2 is also associated with the production of cyclopentenone prostaglandins. Consequently, inhibition of COX-2 may interfere with the full resolution of inflammation, potentially promoting the persistence of activated immune cells in tissues and leading to chronic, "smoldering" inflammation. This effect may be responsible for the increased incidence of cardiovascular disease in patients using selective COX-2 inhibitors for long periods of time.

In one aspect, the compounds disclosed herein may be used to control the production of pro-inflammatory cytokines within the cell by selectively activating regulatory cysteine residues (RCRs) on proteins that regulate the activity of redox-sensitive transcription factors. Activation of RCRs by cyPGs has been shown to initiate a proresolution program in which the activity of the antioxidant and cytoprotective transcription factor Nrf2 is potently induced and the activities of the pro-oxidant and pro-inflammatory transcription factors NF-κB and the STATs are suppressed. In some embodiments, this increases the production of antioxidant and reductive molecules (NQO1, HO-1, SOD1, γ-GCS) and decreases oxidative stress and the production of pro-oxidant and pro-inflammatory molecules (iNOS, COX-2, TNF-α). In some embodiments, the compounds of this invention may cause the cells that host the inflammatory event to revert to a non-inflammatory state by promoting the resolution of inflammation and limiting excessive tissue damage to the host.

V. PHARMACEUTICAL FORMULATIONS AND ROUTES OF ADMINISTRATION

The compounds of the present disclosure may be administered by a variety of methods, e.g., orally or by injection (e.g. subcutaneous, intravenous, intraperitoneal, etc.). Depending on the route of administration, the active compounds may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound. They may also be administered by continuous perfusion/infusion of a disease or wound site.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a patient in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., 1984).

The therapeutic compound may also be administered parenterally, intraperitoneally, intraspinally, or intracerebrally. Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Pharmaceutical compositions suitable for injectable use include: sterile aqueous solutions (where water soluble), dispersions, and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. See for example U.S. patent application by J. Zhang, entitled "Amorphous Solid Dispersions of CDDO-Me for Delayed Release Oral Dosage Compositions," filed Feb. 13, 2009, which is incorporated herein by reference. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile carrier which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient (i.e., the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and

uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of a selected condition in a patient.

The therapeutic compound may also be administered topically to the skin, eye, or mucosa. Alternatively, if local delivery to the lungs is desired the therapeutic compound may be administered by inhalation in a dry-powder or aerosol formulation.

Active compounds are administered at a therapeutically effective dosage sufficient to treat a condition associated with a condition in a patient. For example, the efficacy of a compound can be evaluated in an animal model system that may be predictive of efficacy in treating the disease in humans, such as the model systems shown in the examples and drawings.

The actual dosage amount of a compound of the present disclosure or composition comprising a compound of the present disclosure administered to a subject may be determined by physical and physiological factors such as age, sex, body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiopathy of the subject and on the route of administration. These factors may be determined by a skilled artisan. The practitioner responsible for administration will typically determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject. The dosage may be adjusted by the individual physician in the event of any complication.

An effective amount typically will vary from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 100 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, from about 10.0 mg/kg to about 150 mg/kg in one or more dose administrations daily, for one or several days (depending of course of the mode of administration and the factors discussed above). Other suitable dose ranges include 1 mg to 10000 mg per day, 100 mg to 10000 mg per day, 500 mg to 10000 mg per day, and 500 mg to 1000 mg per day. In some particular embodiments, the amount is less than 10,000 mg per day with a range of 750 mg to 9000 mg per day.

The effective amount may be less than 1 mg/kg/day, less than 500 mg/kg/day, less than 250 mg/kg/day, less than 100 mg/kg/day, less than 50 mg/kg/day, less than 25 mg/kg/day or less than 10 mg/kg/day. It may alternatively be in the range of 1 mg/kg/day to 200 mg/kg/day. For example, regarding treatment of diabetic patients, the unit dosage may be an amount that reduces blood glucose by at least 40% as compared to an untreated subject. In another embodiment, the unit dosage is an amount that reduces blood glucose to a level that is ±10% of the blood glucose level of a non-diabetic subject.

In other non-limiting examples, a dose may also comprise from about 1 microgram/kg/body weight, about 5 microgram/kg/body weight, about 10 microgram/kg/body weight, about 50 microgram/kg/body weight, about 100 microgram/kg/body weight, about 200 microgram/kg/body weight, about 350 microgram/kg/body weight, about 500 microgram/kg/body weight, about 1 milligram/kg/body weight, about 5 milligram/kg/body weight, about 10 milligram/kg/body weight, about 50 milligram/kg/body weight, about 100 milligram/kg/body weight, about 200 milligram/kg/body weight, about 350 milligram/kg/body weight, about 500 milligram/kg/body weight, to about 1000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples of a derivable range from the numbers listed herein, a range of about 5 mg/kg/body weight to about 100 mg/kg/body weight, about 5 microgram/kg/body weight to about 500 milligram/kg/body weight, etc., can be administered, based on the numbers described above.

In certain embodiments, a pharmaceutical composition of the present disclosure may comprise, for example, at least about 0.1% of a compound of the present disclosure. In other embodiments, the compound of the present disclosure may comprise between about 2% to about 75% of the weight of the unit, or between about 25% to about 60%, for example, and any range derivable therein.

Single or multiple doses of the agents are contemplated. Desired time intervals for delivery of multiple doses can be determined by one of ordinary skill in the art employing no more than routine experimentation. As an example, subjects may be administered two doses daily at approximately 12 hour intervals. In some embodiments, the agent is administered once a day.

The agent(s) may be administered on a routine schedule. As used herein a routine schedule refers to a predetermined designated period of time. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. For instance, the routine schedule may involve administration twice a day, every day, every two days, every three days, every four days, every five days, every six days, a weekly basis, a monthly basis or any set number of days or weeks there-between. Alternatively, the predetermined routine schedule may involve administration on a twice daily basis for the first week, followed by a daily basis for several months, etc. In other embodiments, the invention provides that the agent(s) may be taken orally and that the timing of which is or is not dependent upon food intake. Thus, for example, the agent can be taken every morning and/or every evening, regardless of when the subject has eaten or will eat.

VI. COMBINATION THERAPY

In addition to being used as a monotherapy, the compounds of the present invention may also find use in combination therapies. Effective combination therapy may be achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, administered at the same time, wherein one composition includes a compound of this invention, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

Non-limiting examples of such combination therapy include combination of one or more compounds of the invention with another anti-inflammatory agent, a chemotherapeutic agent, radiation therapy, an antidepressant, an antipsychotic agent, an anticonvulsant, a mood stabilizer, an anti-infective agent, an antihypertensive agent, a cholesterol-lowering agent or other modulator of blood lipids, an agent for promoting weight loss, an antithrombotic agent, an agent for treating or preventing cardiovascular events such as myocardial infarction or stroke, an antidiabetic agent, an agent for reducing transplant rejection or graft-versus-host disease, an anti-arthritic agent, an analgesic agent, an anti-asthmatic agent or other treatment for respiratory diseases, or an agent

for treatment or prevention of skin disorders. Compounds of the invention may be combined with agents designed to improve a patient's immune response to cancer, including (but not limited to) cancer vaccines. See Lu et al. (2011), which is incorporated herein by reference.

VII. EXAMPLES

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Methods and Materials

Nitric Oxide Production and Cell Viability Assay.

RAW264.7 mouse macrophages were plated in 96-well plates at 30,000 cells/well in triplicate in RPMI1640+0.5% FBS and incubated at 37° C. with 5% CO_2. On the next day, cells were pretreated with DMSO or drug (0-200 nM dose range) for 2 hours, and then treated with recombinant mouse IFNγ (R&D Systems) for 24 hours. Nitric Oxide concentration in media was determined using the Griess reagent system (Promega). Cell viability was determined using WST-1 reagent (Roche). IC_{50} values were determined based on the suppression of IFNγ induced Nitric Oxide production normalized to cell viability.

NQO1-ARE *Luciferase* Reporter Assay.

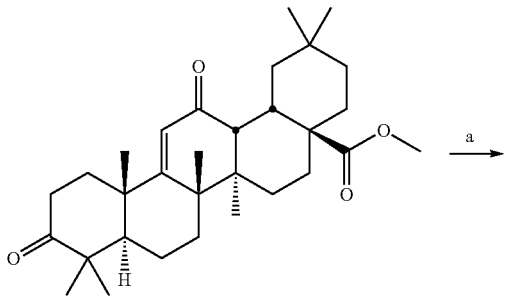
This assay allows for quantitative assessment of the endogenous activity of the Nrf2 transcription factor in cultured mammalian cells. Expression of *Firefly luciferase* from NQO1-ARE *luciferase* reporter plasmid is controlled by binding of Nrf2 to a specific enhancer sequence corresponding to the antioxidant response element (ARE) that was identified in the promoter region of the human NADPH:quinone oxidoreductase 1 (NQO1) gene (Xie et al., 1995). The plasmid was constructed by inserting a sequence:

5'-CAGTCACAGTGACTCAGCAGAATCTG-3' (SEQ ID NO: 1)

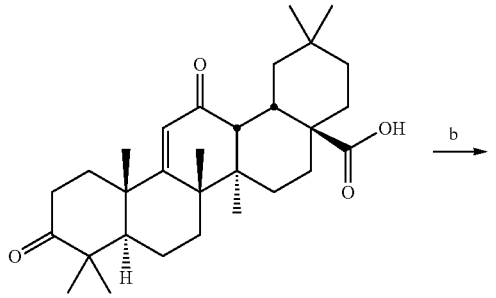
encompassing the human NQO1-ARE into the pLuc-MCS vector using HindIII/XhoI cloning sites (GenScript Corp., Piscataway, N.J.). The assay is performed in HuH7 cells maintained in DMEM (Invitrogen) supplemented with 10% FBS and 100 U/mL (each) of penicillin and streptomycin. For the assay, cells are plated in 96-well plates at 17,000 cells per well. Twenty four hours later, the cells are co-transfected with 50 ng each of NQO1-ARE reporter plasmid and pRL-TK plasmid using Lipofectamine 2000 transfection reagent (Invitrogen). pRL-TK plasmid constitutively expresses *Renilla luciferase* and is used as an internal control for normalization of transfection levels. Thirty hours after transfection, the cells are treated with compounds (at concentrations ranging from 0 to 1 μM) for eighteen hours. *Firefly* and *Renilla luciferase* activity is assayed by Dual-Glo *Luciferase* Assay (Promega Corp., Madison, Wis.), the luminescence signal is measured on an L-Max II luminometer (Molecular Devices). *Firefly luciferase* activity is normalized to the *Renilla* activity, and fold induction over a vehicle control (DMSO) of normalized *Firefly* activity is calculated. The fold induction at 62.5 nM concentration is used for comparing relative potencies of compounds to induce Nrf2 transcriptional activity. See Xie et al., 1995, which is incorporated herein by reference.

Synthetic Schemes, Reagents and Yields

Scheme 1a



1



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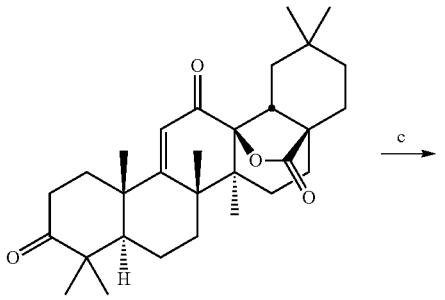

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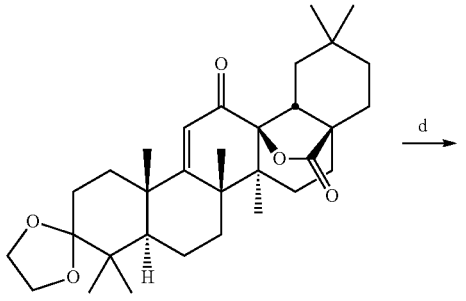

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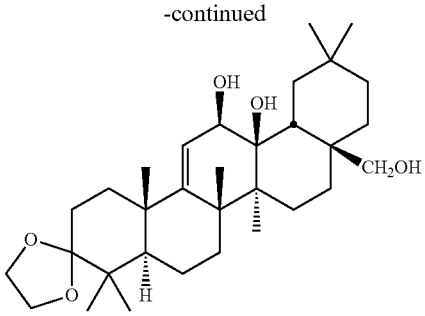

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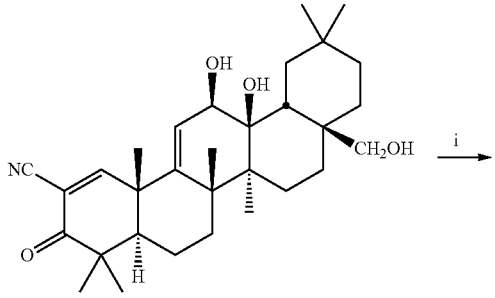
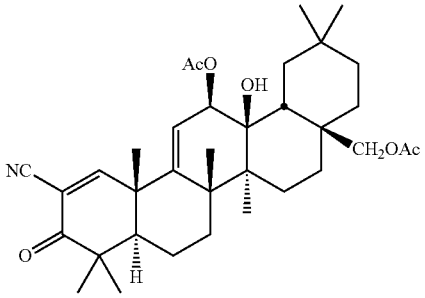


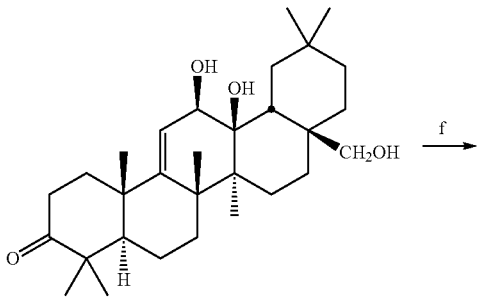
TX63489



TX63498

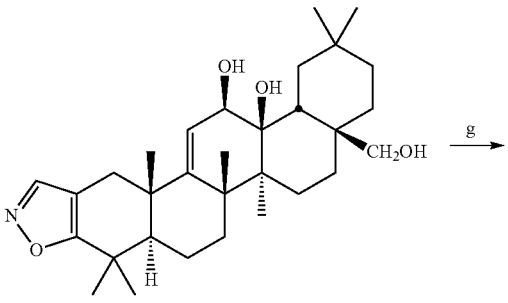
Reagents and conditions: (a) LiI, DMF, 160° C., 6 h, 89%; (b) PhI(OH)OTs, CH_2Cl_2, reflux, 16 h, 36%; (c) Ethylene glycol, p-TsOH, Toluene, reflux, 1 h, 69%; (d) $LiAlH_4$, THF, reflux, 1.5 h; (e) PTSA, Acetone, THF, H_2O, 20 h, rt, 91%; (f) 1)HCOOEt, NaOMe, rt, 1 h, 2) NH_2OH HCl, EtOH, H_2O, 55° C., 4 h, 51%; (g) NaOMe, MeOH, 55° C., 2 h, 80%; (h) DBDMH, DMF, 0° C., 2 h then pyridine, 55° C., 4 h, 72%; (i) Ac_2O, pyridine, 0° C. to rt, 5 h, 55%.

Scheme 1b



6

Scheme 2



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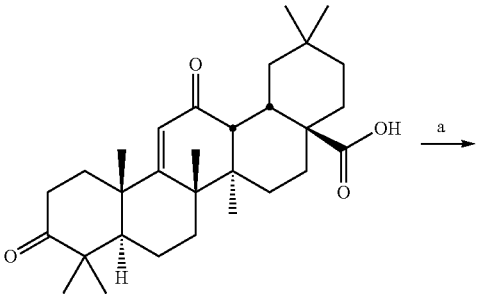

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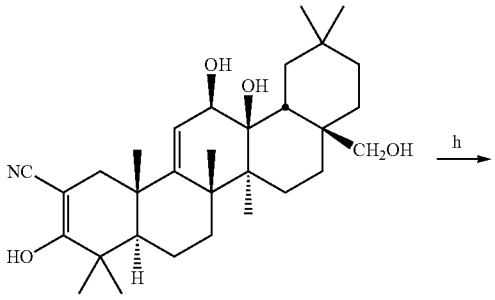

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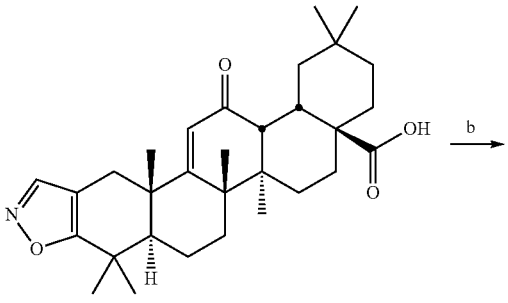

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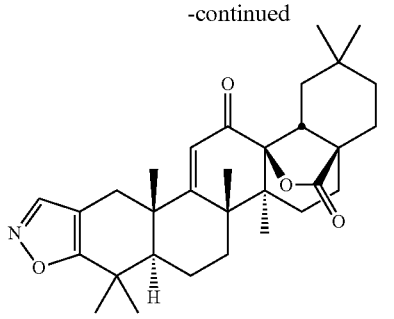

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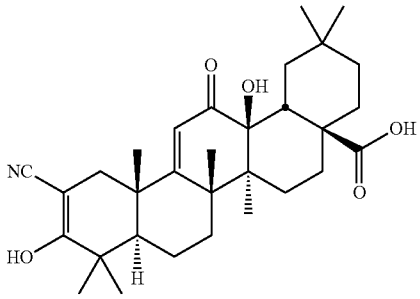

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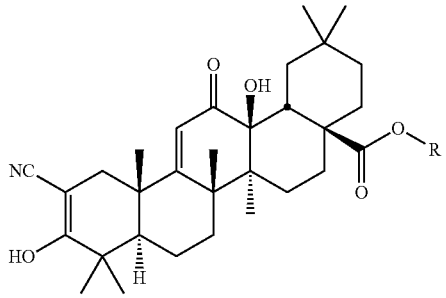
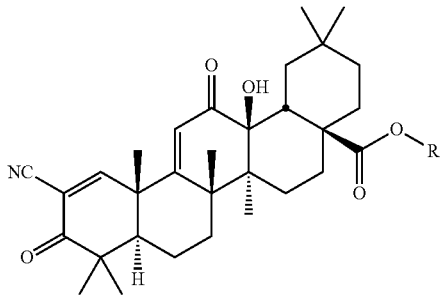


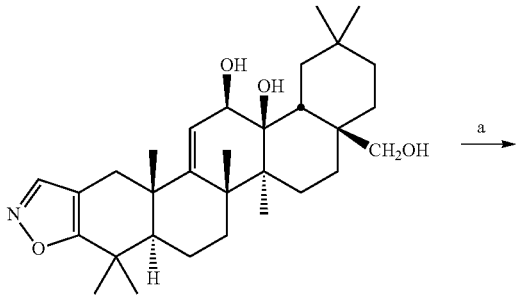
12a: R = Me
12b: R = Et



TX63421: R = Me
TX63469: R = Et

Reagents and conditions: (a) 1) HCOOEt, NaOMe, MeOH, 1 h; 2) NH_2OH HCl, EtOH, H_2O, 55° C., 4 h, 89%; (b) PhI(OH)OTs, CH_2Cl_2, reflux, 2 h, 38%; (c) NaOH, EtOH, THF, H_2O, rt, 6 h, 77%; (d) for 12a: $TMSCHN_2$, MeOH, toluene, 0° C., 10 min, 64%; for 12b: Diazoethane (prepared in situ from N-nitroso-N-ethylurea, KOH and MTBE), MTBE, $CHCl_3$, 0° C., 66%; (e) DBDMH, DMF, 0° C., 2 h then pyridine, 55° C., 4 h, for TX63421: 66%, for TX63469: 71%.

Scheme 3



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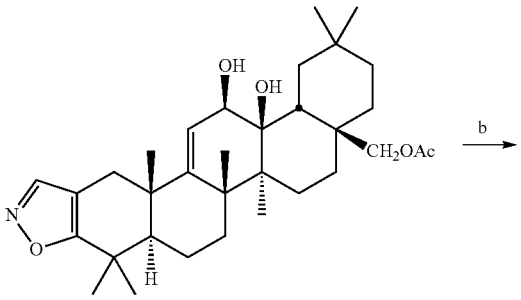

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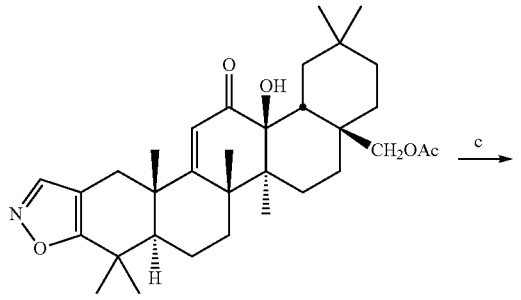

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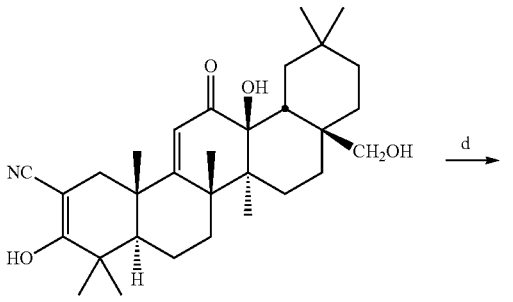

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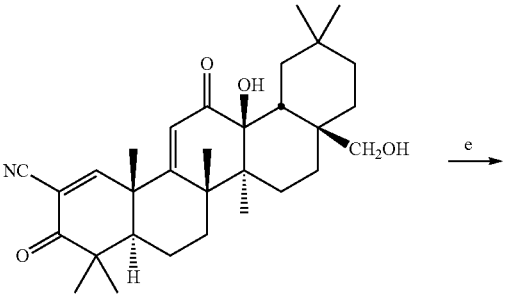

TX63490

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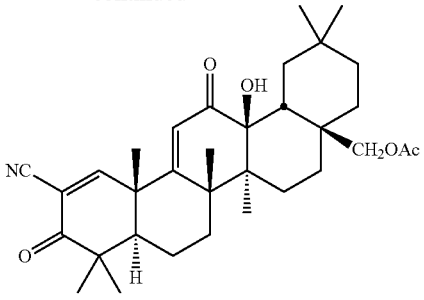
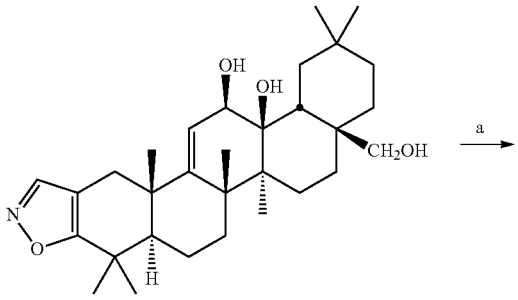


TX63499

Reagents and conditions: (a) Ac_2O, pyridine, 0° C. to rt, 2.5 h, 68%; (b) TPAP, NMO, 4Å MS, rt, 1 h, 89%; (c) NaOMe, MeOH, 55° C., 2 h, 89%; (d) DBDMH, DMF, 0° C., 2 h then pyridine, 55° C., 4 h, 67%; (e) Ac_2O, pyridine, DMAP, rt, 5 min, 56%.

Scheme 4



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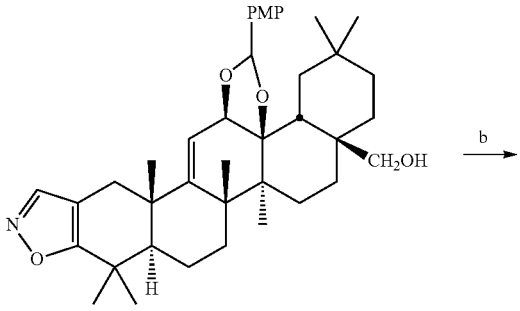

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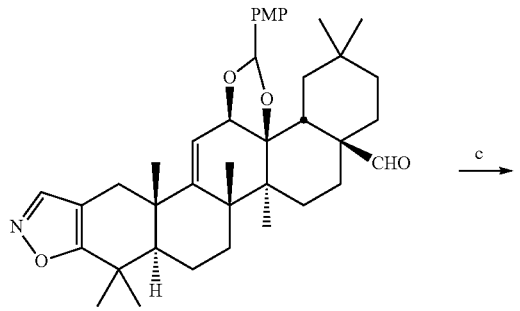

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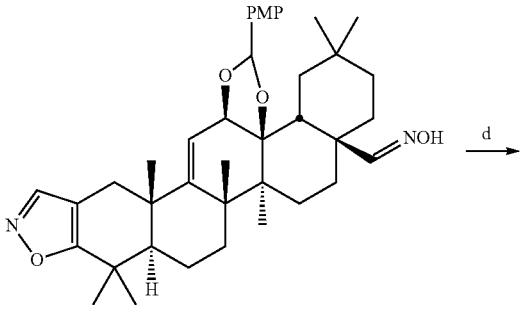

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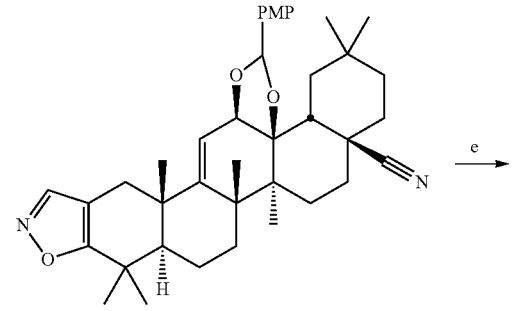

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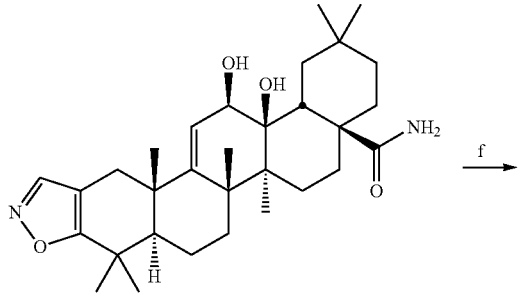

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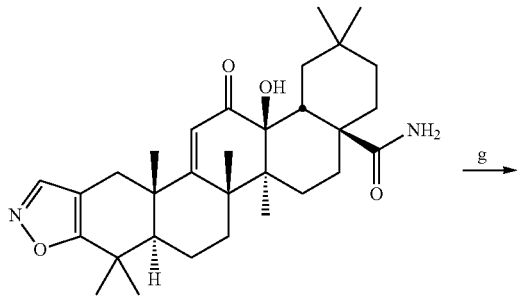

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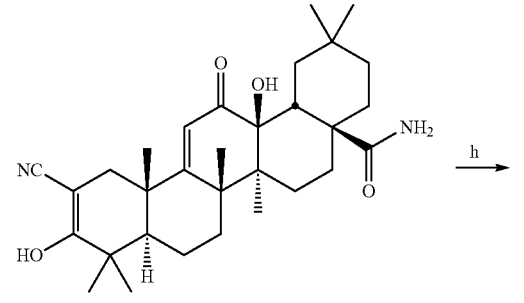

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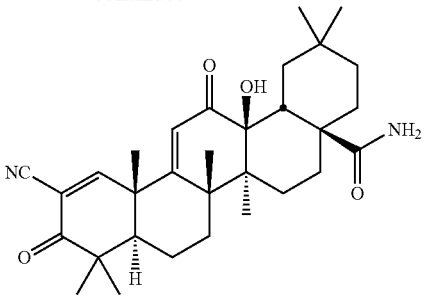
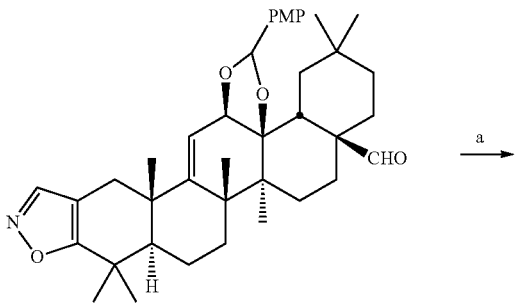


TX63530

Reagents and conditions: (a) 4-(MeO)PhCH(OMe)$_2$, p-TsOH, DCM, DMF, rt, 1 h, 98%; (b) TPAP, NMO, 4Å MS, 1 h, rt, 95%; (c) NH_2OH HCl, NaOAc, EtOH, reflux, 5 h, 98%; (d) TEA, TFAA, microwave, 100° C., 30 min, 97%; (e) TFA, DCM, H_2O, rt, 1 h, 71%; (f) TPAP, NMO, 4Å MS, rt, 3.5 h, 19%; (g) NaOMe, MeOH, 55° C., 1 h, 60%; (h) DBDMH, DMF, 0° C., 1 h then pyridine, 55° C., 4 h, 28%.

Scheme 5



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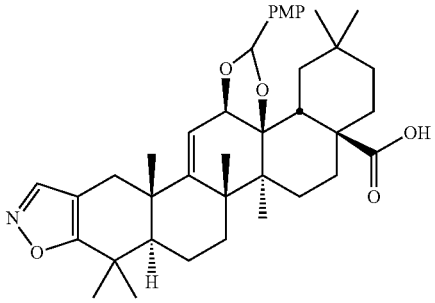

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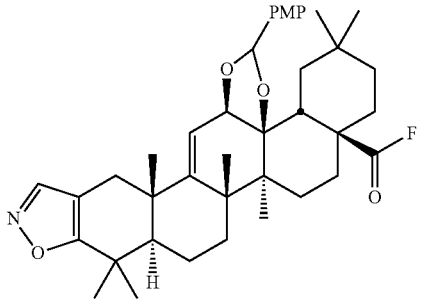

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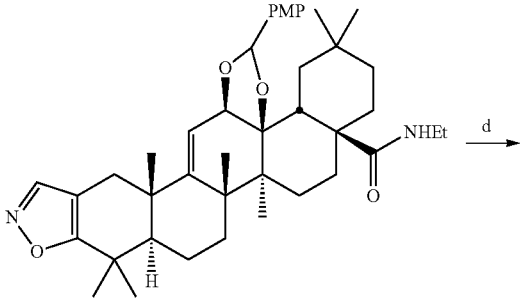

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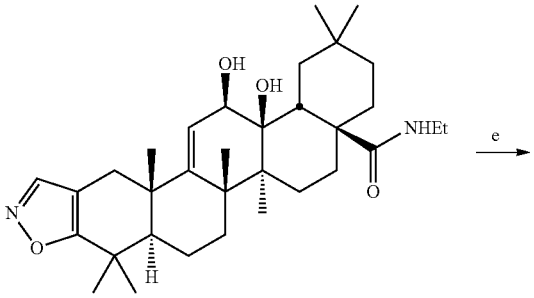

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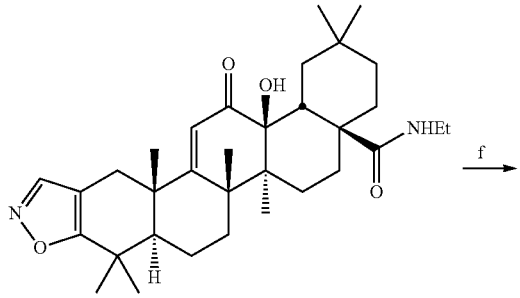

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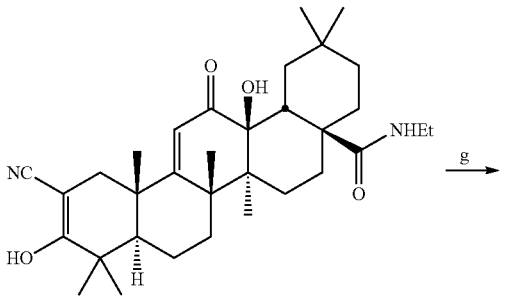

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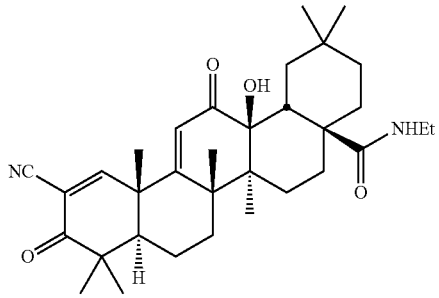
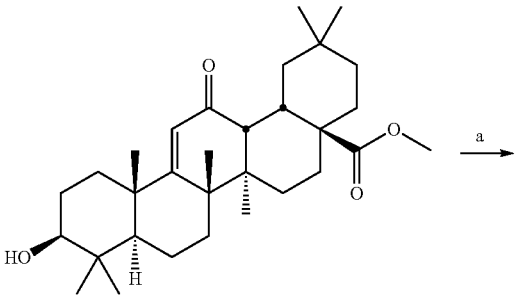


TX63536

Reagents and conditions: (a) $NaClO_2$, tBuOH, H_2O, NaH_2PO_4, 2-Me-2-butene, rt, 16 h, 67%; (b) Et_2NSF, CH_2Cl_2, rt, 15 min, 60%; (c) $EtNH_2$, THF, microwave, 17 h, 100° C., 49%; (d) TFA, H_2O, EtOH, 1 h, 85%; (e) TPAP, NMO, 4Å MS, 1 h, 75%; (f) NaOMe, MeOH, 55° C., 1 h, 65%; (g) DBDMH, DMF, 0° C., 2 h then pyridine, 55° C., 4 h, 53%.

Scheme 6a



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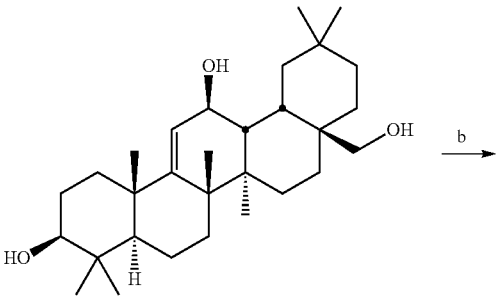

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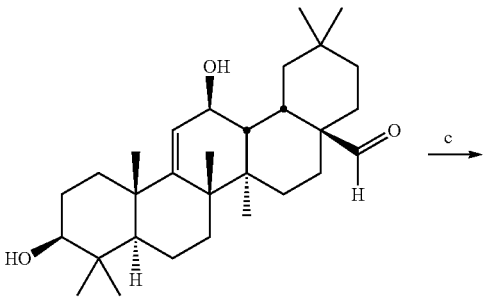

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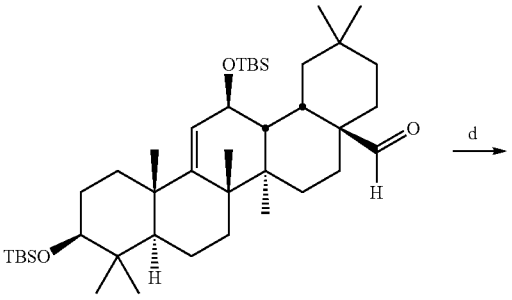

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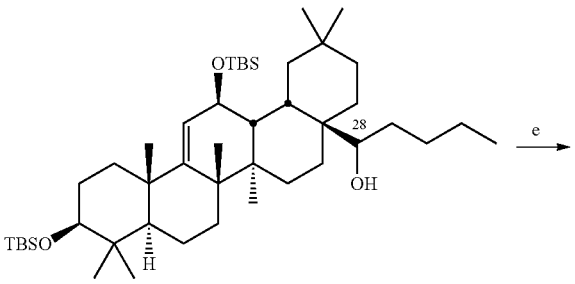
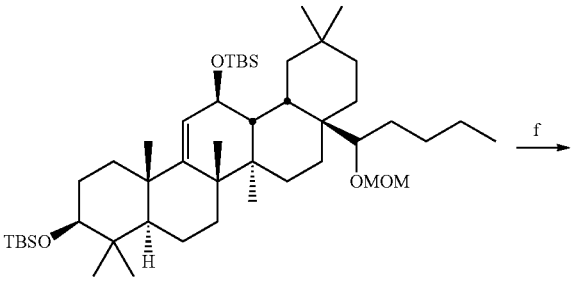
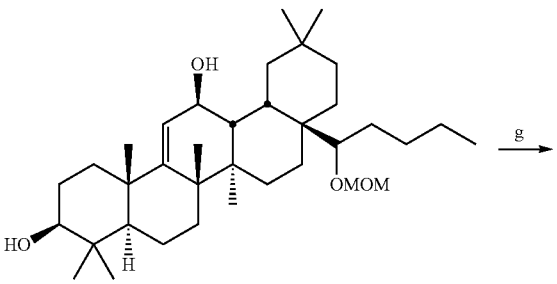


33A, 33B
two isomers at C28



34A, 34B

Scheme 6b



35A, 35B

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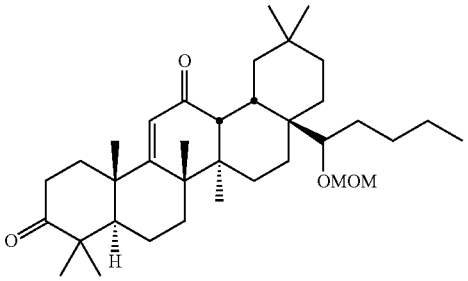
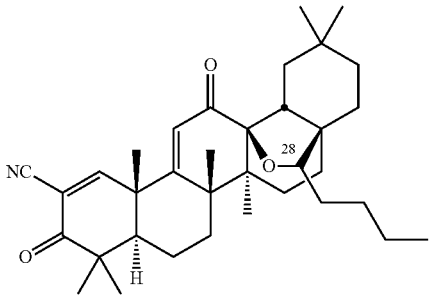
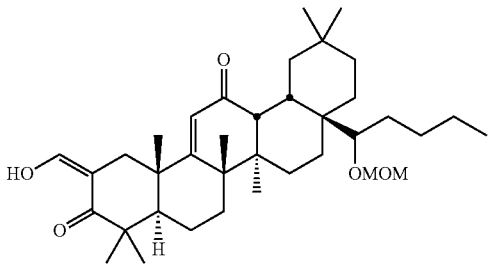


36A, 36B



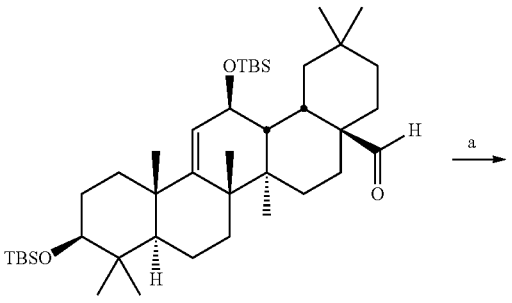
TX63481, TX63484
two isomers at C28

Reagents and conditions: (a) $LiAlH_4$, THF, 0° C., to reflux, 2 h, 53%; (b) $PhI(OAc)_2$, TEMPO, H_2O, CH_2Cl_2, rt, 2 d, 70%; (c) TBSCl, imidazole, DMF, rt, 18 h, 86%; (d) n-BuLi, THF, -78° C., 20 min, two isomers obtained as 33A: 55%, 33B: 42%; (e) MOMCl, DIPEA, CH_2Cl_2, rt, 2 d; (f) TBAF, THF, 50° C., 16 h, 35A: 96%, 35B: quantitative for two steps; (g) TPAP, NMO, 4Å MS CH_2Cl_2, rt, 1 h, 36A: 83%, 36B: 84%; (h) HCOOEt, NaOMe, 0° C., 4 h; (i) NH_2OH•HCl, EtOH, H_2O, 55° C., overnight, then HCl, 1,4-dioxane, 55° C., 5 d, A: 28%, B: 34% for two steps; (j) NaOMe, MeOH, 55° C.; (k) DBDMH, DMF, then pyridine, 55° C., A: 72%, B: 78% for two steps.

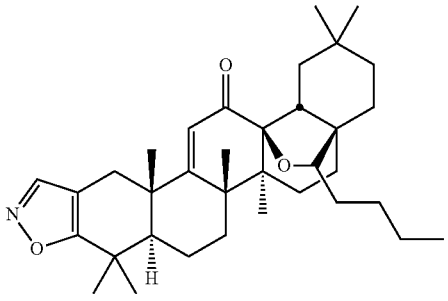


37A, 37B

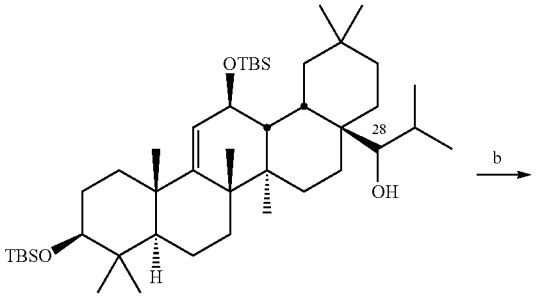
Scheme 7



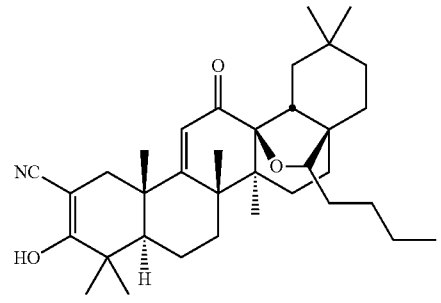
32



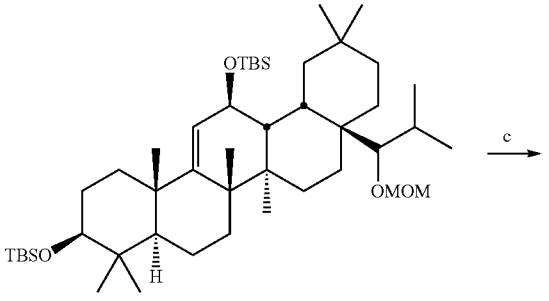
38A, 38B



40A & 40B
two isomers at C28

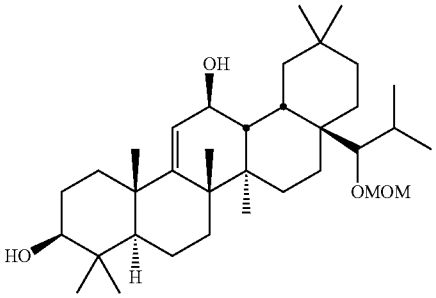


39A, 39B



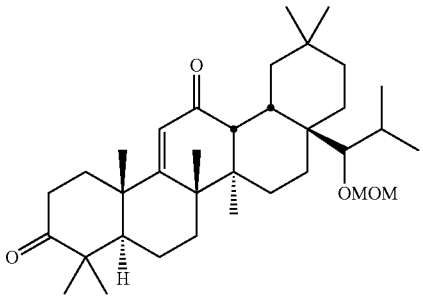
41
A isomer at C28

-continued



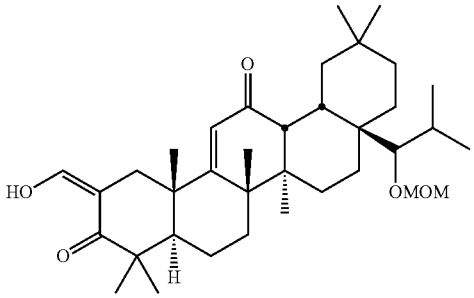
d

42



e

43



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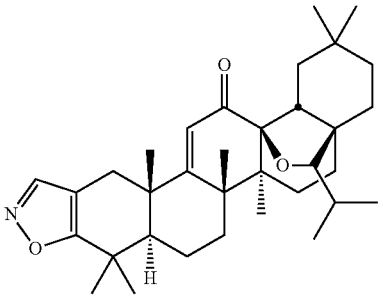
44



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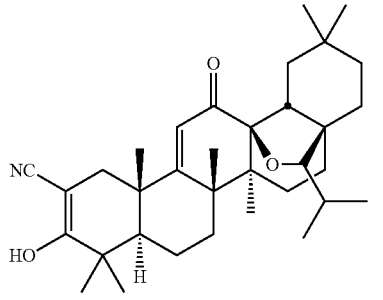
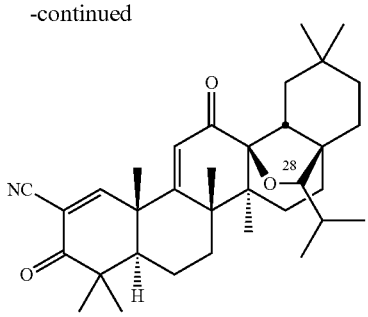
45



h

46

-continued



TX63496
A isomer at C28

Reagents and conditions: (a) i-PrLi/pentane, THF, -78° C., 2 h, two isomers obtained as A: 51%, B: 40%; (b) MOMCl, DIPEA, CH_2Cl_2, reflux, 2 d; (c) TBAF, THF, 50° C., 23 h, 83% for two steps; (d) TPAP, NMO, 4Å MS CH_2Cl_2, rt, 1.5 h, 86%; (e) HCOOEt, NaOMe, 0° C. to rt, 7 h; (f) NH_2OH•HCl, EtOH, H_2O, 55° C., 6 h, then HCl, 1,4-dixane, 55° C., 3 d, 14% for two steps; (g) NaOMe, MeOH, 55° C., 6.5 h; (h) DBDMH, DMF, 0° C. to rt, 6 h, then pyridine, 55° C. 18.5 h, 65% for two steps.

Synthesis and Characterization of Compounds and Intermediates

Compound 2:

Compound 1 (3 g) and LiI (16.7 g) were dissolved in 45 mL DMF. The mixture was stirred at 160° C. for 6 hours while nitrogen was bubbled through the solution. The reaction mixture was diluted with EtOAc, and then washed by 1 N HCl solution, H_2O and Na_2SO_3 solution. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-100% EtOAc in Hexane) to give compound 2 (2.59 g, 89%) as white solid: m/z=469.3 (M+1).

Compound 3:

Compound 2 (890 mg) and PhI(OH)(OTs) (818 mg) were dissolved in 38 mL CH_2Cl_2 in a round bottom flask. The bottle was sealed and the mixture was heated and refluxed for 16 hr until no starting material detected by TLC. The reaction mixture was cooled to room temperature and the white precipitates were filtered off. The filtrate was concentrated and the residue was purified by flash chromatography (silica gel, 35% EtOAc in Hexane) to give compound 3 (318 mg, 36%) as yellow solid: m/z=467.3 (M+1).

Compound 4:

Compound 3 (158 mg), ethylene glycol (0.20 mL) and p-TsOH (16 mg) were mixed in 6 mL toluene. The mixture was refluxed for 1 hr using a Dean-Stark condenser. After cooling to room temperature, the mixture was washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-35% EtOAc in Hexane) to give compound 4 (120 mg, 69%) as white solid: m/z=511.3 (M+1).

Compound 5:

To a solution of compound 4 (117 mg) in 2.3 mL THF was added $LiAlH_4$ (2.0 M in THF, 343 μL). The mixture was refluxed for 1.5 hr. After cooling to 0° C., the mixture was quenched by EtOH, diluted with EtOAc and washed by 1 N HCl and H_2O. The organic phase was dried over $MgSO_4$ and concentrated to give compound 5 (116 mg) as white solid: m/z=499.3 (M+1).

Compound 6:

To a solution of compound 5 (15 mg) in 0.29 mL THF and 0.29 mL acetone was added a solution of PTSA (5.5 mg) in 48 μL H_2O. The mixture was stirred at room temperature for 20

hr. After diluting with EtOAc, the reaction mixture was washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-40% EtOAc in Hexane) to give compound 6 (13 mg, 91%) as white solid: m/z=473.3 (M+1).

Compound 7:

To a solution of compound 6 (13 mg) in 68 μL HCOOEt was added a solution of NaOMe (25% in MeOH, 95 μL) at 0° C. The mixture was stirred at room temperature for 1 hr. After diluting with MTBE, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was dissolved in 0.55 mL EtOH and 0.11 mL H_2O and NH_2OH—HCl (2.9 mg) was added. The mixture was heated to 55° C. and stirred for 4 hr. After diluting with EtOAc, the reaction mixture was washed by H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 30% EtOAc in Hexane) to give compound 7 (7.0 mg, 51%) as white solid: m/z=498.3 (M+1).

Compound 8:

To a solution of compound 7 (7 mg) in 0.14 mL MeOH was added a solution of NaOMe (25% in MeOH, 6.4 μL). The mixture was heated to 55° C. and stirred for 2 hr. After diluting with MTBE, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-40% EtOAc in Hexane) to give compound 8 (5.6 mg, 80%) as white solid: m/z=480.3 (M-H_2O+1).

Compound TX63489:

To a solution of compound 8 (5.6 mg) in 58 μL DMF was added DBDMH (1.7 mg) at 0° C. The mixture was stirred for 1 hr at 0° C. After 1 hr, the reaction mixture was added by pyridine (2.8 μL) and was heated to 55° C. and stirred for 4 hr. After diluting with EtOAc, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 40% EtOAc in Hexane) to give compound TX63489 (4 mg, 72%) as white glass: ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 5.41 (br d, J=2.2 Hz, 1H), 4.28 (br d, J=6.3 Hz, 1H), 3.91 (d, J=10.7 Hz, 1H), 3.56 (d, J=10.7 Hz, 1H), 3.13 (m, 1H), 2.30 (td, J=13.7, 3.7 Hz, 1H), 2.14 (br d, J=8.4 Hz, 1H), 1.89-1.02 (m, 16H), 1.51 (s, 3H), 1.48 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H); m/z=496.3 (M+1).

Compound TX63498:

To a solution of compound TX63489 (37 mg) in 0.75 mL pyridine was added Ac_2O (35 μL) at 0° C. The mixture was stirred for 1 hr at 0° C., then 4 hr at room temperature. The reaction mixture was quenched by sat. $NaHCO_3$ solution and extracted by EtOAc. The organic phase was washed by 1 N HCl solution and H_2O, then dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-15% EtOAc in DCM) to give compound TX63498 (24 mg, 55%) as white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.47 (s, 1H), 5.27 (s, 1H), 4.76 (d, J=11.2 Hz, 1H), 4.06 (d, J=11.2 Hz, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.18-1.04 (m, 17H), 1.51 (s, 3H), 1.49 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.89 (s, 3H), 0.81 (S, 3H); m/z=520.3 (M−AcOH+1).

Compound 9:

To a solution of compound 2 (1.0 g) in 5.2 mL HCOOEt was added a solution of NaOMe (25% in MeOH, 7.3 mL) at 0° C. The mixture was stirred at room temperature for 1 hr. After diluting with MTBE, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was dissolved in 20 mL EtOH and 2.0 mL H_2O and NH_2OH—HCl (224 mg) was added. The mixture was heated to 55° C. and stirred for 4 hr. After diluting with EtOAc, the reaction mixture was washed by H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 30% EtOAc in Hexane) to give compound 9 (940 mg, 89%) as white solid: m/z=494.3 (M+1).

Compound 10:

Compound 9 (500 mg) and PhI(OH)(OTs) (478 mg) were dissolved in 10 mL CH_2Cl_2 in a round bottom flask. The mixture was heated and refluxed for 2 hr. The reaction mixture was cooled to room temperature and was concentrated. The residue was purified by flash chromatography (silica gel, 0-50% EtOAc in Hexane) to give compound 10 (190 mg, 38%) as white solid: m/z=492.3 (M+1).

Compound 11:

Compound 10 (15 mg) was dissolved in a mixture of 0.4 mL EtOH, 0.2 mL THF and 0.05 mL H_2O. Then NaOH solution (10%, 61 μL) was added.

The mixture was stirred at room temperature for 6 hr. After diluting with MTBE, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated to give crude compound 11 (12 mg, 77%) as white solid: m/z=492.3 (M-H_2O+1).

Compound 12a:

Compound 11 (12 mg) was dissolved in a mixture of 0.2 mL MeOH and 0.6 mL toluene. Then $TMSCHN_2$ (23 μL) was added at 0° C. The mixture was stirred at 0° C. for 10 min. After quenching with AcOH, the reaction mixture was diluted with EtOAc, washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-25% EtOAc in Hexane) to give compound 12a (8.2 mg, 64%) as white solid: m/z=506.3 (M-H_2O+1).

Compound TX63421:

To a solution of compound 12a (8.2 mg) in 100 μL DMF was added DBDMH (2.2 mg) at 0° C. The mixture was stirred for 1 hr at 0° C. After 1 hr, the reaction mixture was added by pyridine (4 μL) and was heated to 55° C. and stirred for 4 hr. After diluting with EtOAc, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-25% EtOAc in Hexane) to give compound TX63421 (5.4 mg, 66%) as white glass: ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 5.99 (s, 1H), 3.70 (s, 3H), 2.89 (br d, J=11.8 Hz, 1H), 2.26 (td, J=13.1, 3.8 Hz, 1H), 1.99-1.83 (m, 3H), 1.77-1.70 (m, 4H), 1.63-1.56 (m, 2H), 1.52 (s, 3H), 1.50 (s, 3H), 1.45-1.09 (m, 6H), 1.26 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.89 (S, 3H); m/z=504.3 (M-H_2O+1).

Compound 12b:

N-Nitroso-N-ethylurea (313 mg, 64% purity) was dissolved in 1.7 mL MTBE. KOH (40%) solution (made from 0.52 g KOH and 0.8 mL H_2O) were added at 0° C. The mixture was stirred at 0° C. for 15 min and the upper layer was removed and dried over KOH. The prepared diazoethane solution was kept at 0° C. before use.

Compound 11 (33 mg) was dissolved in a mixture of 0.7 mL MTBE and 0.7 mL $CHCl_3$. Then diazoethane solution was added dropwise at 0° C. 20 drops of diazoethane solution was added during 15 min period. When TLC showed the reaction is finished, the reaction was quenched with AcOH. The reaction mixture was diluted with EtOAc, washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash

chromatography (silica gel, 0-35% EtOAc in Hexane) to give compound 12b (23 mg, 66%) as white solid: m/z=520.3 (M-H_2O+1).

Compound TX63469:

To a solution of compound 12b (22.5 mg) in 210 μL DMF was added DBDMH (6 mg) at 0° C. The mixture was stirred for 1 hr at 0° C. After 1 hr, the reaction mixture was added by pyridine (10 μL) and was heated to 55° C. and stirred for 4 hr. After diluting with EtOAc, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-25% EtOAc in Hexane) to give compound TX63469 (16 mg, 71%) as white glass: ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 5.98 (s, 1H), 4.27-4.10 (m, 2H), 2.88 (br d, J=12.4 Hz, 1H), 2.26 (td, J=13.2, 3.6 Hz, 1H), 1.99-1.09 (m, 15H), 1.52 (s, 3H), 1.50 (s, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.89 (S, 3H); m/z=518.3 (M-H_2O+1).

Compound 13:

To a solution of compound 7 (35 mg) in 0.7 mL pyridine was added Ac_2O (37 μL) at 0° C. The mixture was stirred for 1 hr at 0° C., then 2.5 hr at room temperature. The reaction mixture was quenched by sat. $NaHCO_3$ solution and extracted by EtOAc. The organic phase was washed by 1 N HCl solution and H_2O, then dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-35% EtOAc in Hexane) to give compound 13 (27 mg, 68%) as white solid: m/z=540.4 (M+1).

Compound 14:

To a solution of compound 13 (27 mg) in 1 mL CH_2Cl_2 was added NMO (9 mg), 4 Å MS (2 beads) and TPAP (2 mg). The mixture was stirred for 1 hr at room temperature. The reaction mixture was concentrated. The residue was purified by flash chromatography (silica gel, 0-30% EtOAc in Hexane) to give compound 14 (23 mg, 89%) as white solid: m/z=538.3 (M+1).

Compound 15:

To a solution of compound 14 (21.5 mg) in 0.4 mL MeOH was added a solution of NaOMe (25% in MeOH, 23 μL). The mixture was heated to 55° C. and stirred for 2 hr. The reaction mixture was concentrated. The residue was purified by flash chromatography (silica gel, 0-40% EtOAc in Hexane) to give compound 8 (18 mg, 89%) as white solid: m/z=478.3 (M-H_2O+1).

Compound TX63490:

To a solution of compound 15 (18 mg) in 180 μL DMF was added DBDMH (5.2 mg) at 0° C. The mixture was stirred for 1 hr at 0° C. After 1 hr, the reaction mixture was added by pyridine (9 μL) and was heated to 55° C. and stirred for 4 hr. After diluting with EtOAc, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-35% EtOAc in Hexane) to give compound TX63490 (12 mg, 67%) as white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 5.97 (s, 1H), 4.12 (br d, J=7.7 Hz, 1H), 3.41 (br d, J=9.7 Hz, 1H), 2.87 (br s, 1H), 2.33 (br d, J=11.0 Hz, 1H), 2.14 (td, J=13.5, 3.5 Hz, 1H), 1.93-1.07 (m, 15H), 1.54 (s, 3H), 1.51 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.87 (S, 3H); m/z=476.3 (M-H_2O+1).

Compound TX63499:

To a solution of compound TX63490 (8 mg) in 0.3 mL pyridine was added Ac_2O (20 μL) and DMAP (1 mg) at room temperature. The mixture was stirred for 5 min at room temperature, and then quenched by sat. $NaHCO_3$ solution and extracted by EtOAc. The organic phase was washed by 1 N HCl solution and H_2O, then dried over $MgSO_4$ and concentrated. The residue was purified by PTLC (silica gel, 10% EtOAc in Hexane) to give compound TX63499 (4.9 mg, 56%) as white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 5.98 (s, 1H), 4.37 (d, J=10.7 Hz, 1H), 4.33 (d, J=10.8 Hz, 1H), 2.15-1.13 (m, 17H), 2.10 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.87 (S, 3H); m/z=518.3 (M-H_2O+1).

Compound 16:

To a solution of compound 7 (480 mg) and 4-MeO-PhCH($OMe)_2$ (328 μL) in 9 mL DCM and 3 mL DMF was added p-TsOH (96 mg). The mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with EtOAc, washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-20% EtOAc in Hexane) to give compound 16 (584 mg, containing two epimers, 98%) as white solid: m/z=616.4 (M+1).

Compound 17:

To a solution of compound 16 (383 mg) in 12.5 mL CH_2Cl_2 was added NMO (110 mg), 4 Å MS (500 mg) and TPAP (11 mg). The mixture was stirred for 1 hr at room temperature. The reaction mixture was concentrated. The residue was purified by flash chromatography (silica gel, 0-20% EtOAc in Hexane) to give compound 17 (363 mg, 95%) as white solid: m/z=614.4 (M+1).

Compound 18:

To a solution of compound 17 (330 mg) and NaOAc (176 mg) in 10 mL EtOH was added NH_2OH—HCl (113 mg). The mixture was heated and refluxed for 5 hr. When all starting materials are consumed, the reaction mixture was cooled to room temperature, diluted with EtOAC and washed by H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-25% EtOAc in Hexane) to give compound 18 (330 mg, 98%) as white solid: m/z=629.4 (M+1).

Compound 19:

To a solution of compound 18 (329 mg) in 15 mL THF were added TEA (0.94 mL) and TFAA (0.46 mL). The mixture was stirred at room temperature for 30 min, and then microwaved at 100° C. for 30 min. The reaction mixture was diluted with EtOAC and washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-25% EtOAc in Hexane) to give compound 19 (310 mg, 97%) as white solid: m/z=611.4 (M+1).

Compound 20:

To a solution of compound 19 (191 mg) in 9.5 mL CH_2Cl_2 and 0.3 mL H_2O was added TFA (0.95 mL). The mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with DCM and washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-100% EtOAc in Hexane, then 5% MeOH in DCM) to give compound 20 (113 mg, 71%) as white solid: m/z=493.3 (M-H_2O+1).

Compound 21:

To a solution of compound 20 (113 mg) in 4.5 mL CH_2Cl_2 was added NMO (39 mg), 4 Å MS (250 mg) and TPAP (4 mg). The mixture was stirred for 3.5 hr at room temperature. The reaction mixture was diluted with EtOAc, washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-100% EtOAc in Hexane) to give compound 21 (21 mg, 19%) as white solid: m/z=491.3 (M-H_2O+1).

Compound 22:

To a solution of compound 21 (21 mg) in 0.8 mL MeOH was added a solution of NaOMe (25% in MeOH, 19 μL). The mixture was heated to 55° C. and stirred for 1 hr. The reaction mixture was diluted with MTBE, washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-100% EtOAc in Hexane) to give compound 22 (12.5 mg, 60%) as white solid: m/z=491.3 (M-H_2O+1).

Compound TX63530:

To a solution of compound 22 (12.5 mg) in 130 μL DMF was added DBDMH (3.5 mg) at 0° C. The mixture was stirred for 1 hr at 0° C. After 1 hr, the reaction mixture was added by pyridine (6 μL) and was heated to 55° C. and stirred for 4 hr. After diluting with EtOAc, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by PTLC (silica gel, 0-5% MeOH in EtOAc) to give compound TX63530 (3.5 mg, 28%) as white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.20 (s, 1H), 2.86 (br d, J=11.3 Hz, 1H), 2.10 (td, J=13.3, 5.8 Hz, 1H), 1.92-1.25 (m, 17H), 1.56 (s, 3H), 1.54 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 0.99 (s, 3H), 0.97 (s, 6H); m/z=489.3 (M-H_2O+1).

Compound 23:

Compound 17 (185 mg), NaH_2PO_4 (119 mg), $NaClO_2$ (136 mg) were mixed and dissolved in a mixture of 2-Me-2-butene (3.3 mL), t-BuOH (10 mL) and H_2O (3.3 mL). The mixture stirred for 18 hr at room temperature. When no starting material remained, the reaction mixture was diluted with EtOAc and washed by H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-30% EtOAc in Hexane) to give compound 23 (121 mg, 67%) as white solid: m/z=630.4 (M+1).

Compound 24:

To a solution of compound 23 (155 mg) in 5 mL CH_2Cl_2 was added Et_2NSF_3 (39 μL) dropwise. The mixture was stirred for 15 min. The reaction mixture was diluted with EtOAc, washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-20% EtOAc in Hexane) to give compound 24 (94 mg, 60%) as white solid: m/z=632.4 (M+1).

Compound 25:

To a solution of compound 24 (45 mg) in 0.81 mL THF was added the $EtNH_2$ solution (2.0 M in THF, 1.42 mL). The mixture was microwaved at 100° C. for 17 hr. The reaction mixture was diluted with EtOAc, washed by H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-45% EtOAc in Hexane) to give compound 25 (23 mg, 49%) as white solid: m/z=657.5 (M+1).

Compound 26:

To a solution of compound 25 (23 mg) in 1.35 mL CH_2Cl_2 and 2 drops of H_2O was added TFA (0.14 mL). The mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with DCM and washed by sat. $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-45% EtOAc in Hexane) to give compound 26 (16 mg, 85%) as white solid: m/z=539.4 (M+1).

Compound 27:

To a solution of compound 26 (16 mg) in 0.6 mL CH_2Cl_2 was added NMO (5.3 mg), 4 Å MS (2 beads) and TPAP (1.1 mg). The mixture was stirred for 1 hr at room temperature. The reaction mixture was concentrated. The residue was purified by flash chromatography (silica gel, 0-25% EtOAc in DCM) to give compound 27 (12 mg, 75%) as off-white solid: m/z=537.4 (M+1).

Compound 28:

To a solution of compound 27 (10.7 mg) in 0.4 mL MeOH was added a solution of NaOMe (25% in MeOH, 5.5 μL). The mixture was heated to 55° C. and stirred for 1 hr. The reaction mixture was diluted with MTBE, washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 0-45% EtOAc in Hexane) to give compound 28 (7 mg, 65%) as white solid: m/z=537.4 (M+1).

Compound TX63536:

To a solution of compound 28 (8.4 mg) in 0.1 mL DMF was added DBDMH (2.3 mg) at 0° C. The mixture was stirred for 1 hr at 0° C. After 1 hr, the reaction mixture was added by pyridine (4 μL) and was heated to 55° C. and stirred for 4 hr. After diluting with EtOAc, the reaction mixture was washed by 1 N HCl solution and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 1:5 EtOAc:CH_2Cl_2) to give compound TX63536 (4.5 mg, 53%) as white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 5.96 (s, 1H), 5.85 (br s, 1H), 3.46 (m, 1H), 3.25 (m, 1H), 3.17 (br d, J=12.9 Hz, 1H), 2.15 (td, J=13.0, 2.5 Hz, 1H), 2.14 (td, J=14.4, 3.0 Hz, 1H), 1.90-1.12 (m, 14H), 1.52 (s, 3H), 1.51 (s, 3H), 1.25 (s, 3H), 1.16 (t, J=7.2 Hz, 3H), 1.14 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.88 (S, 3H); m/z=535.3 (M+1).

Compound 30:

Lithium aluminum hydride (2.0 M in THF, 23.3 mL, 46.6 mmol) was added dropwise to a 0° C. solution of compound 29 (5.65 g, 11.7 mmol) in THF (250 mL). After 15 min the solution was warmed to reflux for 1.75 h, cooled to 0° C., and quenched by the successive dropwise addition of 2.5 mL each H_2O, NaOH (4 N), and H_2O at 5 min intervals. The resultant slurry was warmed to room temperature, filtered through a plug of celite, eluted with THF (200 mL), and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound 30 (2.84 g, 53%) as a white solid: m/z=441.4 (M-H_2O+1).

Compound 31:

(Diacetoxyiodo)benzene (2.59 g, 8.04 mmol), TEMPO (0.48 g, 3.1 mmol) and H_2O (2.9 mL) were added sequentially to a room temperature suspension of compound 30 (2.84 g, 6.19 mmol) in CH_2Cl_2 (750 mL). The mixture was vigorously stirred for 17 h, then additional portions of (diacetoxyiodo) benzene (0.78 g, 2.4 mmol) and TEMPO (0.14 g, 0.90 mmol) were added. Stirring was continued for an additional 24 h, then the mixture was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound 31 (1.98 g, 70%) as a white solid: m/z=439.4 (M-H_2O+1).

Compound 32:

A solution of compound 31 (1.98 g, 4.34 mmol), TBSCl (3.28 g, 21.8 mmol) and imidazole (1.20 g, 17.6 mmol) were stirred at room temperature for 18 h. The resultant thick slurry was diluted with EtOAc (400 mL), washed with H_2O (2×100 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 40% EtOAc in hexanes) to give compound 32 (2.57 g, 86%) as a white foam solid.

Compounds 33A and 33B:

A solution of compound 32 (515 mg, 0.752 mmol) in THF (20 mL) was cooled to −78° C., and n-BuLi (2.5 M in hexanes, 1.5 mL, 3.75 mmol) was added. The resultant mixture was stirred at −78° C. for 20 min, quenched by the addition of saturated NH_4Cl (5 mL), and warmed to room temperature

over 20 minutes. The biphasic mixture was diluted with EtOAc (90 mL), washed with H_2O (50 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 40% EtOAc in hexanes) to give compounds 33A (308 mg, 55%) as a glassy solid, and compound 33B (236 mg, 42%) as a white solid.

Compound 34A:

A solution of compound 33A (308 mg, 0.414 mmol), MOMCl (80 μL, 1.05 mmol) and i-Pr_2NEt (0.22 mL, 1.26 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 19 h, then additional MOMCl (40 μL, 0.53 mmol) and i-Pr_2NEt (0.11 mL, 0.63 mmol) were added. The resultant mixture was stirred for an addition 24 h at room temperature, diluted with EtOAc (75 mL), washed with 1M HCl (20 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated to give crude compound 34A (311 mg) as a white solid that was used without further purification.

Compound 34B:

A solution of compound 33B (236 mg, 0.317 mmol), MOMCl (60 μL, 0.79 mmol) and i-Pr_2NEt (0.17 mL, 0.98 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 24 h, then additional MOMCl (30 μL, 0.39 mmol) and i-Pr_2NEt (0.09 mL, 0.5 mmol) were added. The resultant mixture was stirred for an addition 24 h at room temperature, diluted with EtOAc (70 mL), washed with 1M HCl (20 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated to give crude compound 34B (260 mg) as a colorless, viscous oil that was used without further purification.

Compound 35A:

TBAF (1 M in THF, 5.0 mL, 5.0 mmol) was added to a room temperature solution of compound 34A (all above obtained, ≤0.414 mmol) in THF (14 mL), and the mixture was heated to 50° C. for 16 h. The resultant mixture was concentrated to ~5 mL, loaded directly onto silica, and purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound 35A (223 mg, 96% from compound 33A) as a glassy solid.

Compound 35B:

TBAF (1 M in THF, 3.8 mL, 3.8 mmol) was added to a room temperature solution of compound 34B (all above obtained, ≤0.317 mmol) in THF (11 mL), and the mixture was heated to 50° C. for 16 h. The resultant mixture was concentrated to ~5 mL, loaded directly onto silica, and purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound 35B (178 mg, quantitative from compound 33B) as a glassy solid.

Compound 36A:

A mixture of compound 35A (223 mg, 0.399 mmol), NMO (141 mg, 1.20 mmol), 4 Å MS (420 mg) and CH_2Cl_2 (10 mL) was stirred at room temperature for 20 min, then TPAP (14.8 mg, 0.042 mmol) was added in one portion. The resultant mixture was stirred for 1 h, concentrated to ~3 mL, loaded directly onto silica gel, and purified by flash chromatography (silica gel, 0 to 75% EtOAc in hexanes) to give compound 36A (183 mg, 83%) as a white foam solid.

Compound 36B:

A mixture of compound 35B (178 mg, 0.319 mmol), NMO (120 mg, 1.02 mmol), 4 Å MS (328 mg) and CH_2Cl_2 (8 mL) was stirred at room temperature for 20 min, then TPAP (13.2 mg, 0.0376 mmol) was added in one portion. The resultant mixture was stirred for 1 h, concentrated to ~3 mL, loaded directly onto silica gel, and purified by flash chromatography (silica gel, 0 to 70% EtOAc in hexanes) to give compound 36B (149 mg, 84%) as a white foam solid.

Compound 37A:

A solution of sodium methoxide (25% w/w in MeOH, 0.7 mL) was added to a 0° C. suspension of compound 36A (183 mg, 0.330 mmol) in EtOCHO (1.8 mL). The resultant mixture was stirred at 0° C. for 4 h, diluted with EtOAc (70 mL), washed with 1 M HCl (25 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated to give crude compound 37A (200 mg) as a white foam that was used without further purification.

Compound 37B:

A solution of sodium methoxide (25% w/w in MeOH, 0.57 mL) was added to a 0° C. suspension of compound 36B (149 mg, 0.269 mmol) in EtOCHO (1.4 mL). The resultant mixture was stirred at 0° C. for 4 h, diluted with EtOAc (70 mL), washed with 1 M HCl (25 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated to give crude compound 37B (164 mg) as a white foam that was used without further purification.

Compound 38A:

A solution of compound 37A (all above obtained, ≤0.330 mmol) and $NH_2OH.HCl$ (30.6 mg, 0.440 mmol) in a mixture of EtOH (2.4 mL), H_2O (0.45 mL), and THF (0.75 mL) was heated to 55° C. overnight. A solution of HCl (4 M in 1,4-dioxane, 0.1 ml, 0.4 mmol) was added and heating continued for 5 d. The resultant mixture was diluted with EtOAc (60 mL), washed with 1 M HCl (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound 38A (49 mg, 28% from compound 36A) as a glassy solid.

Compound 38B:

A solution of compound 37B (all above obtained, ≤0.269 mmol) and $NH_2OH.HCl$ (25.8 mg, 0.371 mmol) in a mixture of EtOH (2.0 mL), H_2O (0.37 mL), and THF (0.61 mL) was heated to 55° C. overnight. A solution of HCl (4 M in 1,4-dioxane, 0.1 ml, 0.4 mmol) was added and heating continued for 5 d. The resultant mixture was diluted with EtOAc (60 mL), washed with 1 M HCl (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound 38B (49 mg, 34% from compound 36B) as a glassy solid.

Compound 39A:

A solution of compound 38A (49 mg, 0.919 mmol) and sodium methoxide (25% w/w in MeOH, 0.03 mL) in MeOH (1.25 mL) was heated to 55° C. with stirring. After 3 h the mixture was diluted with EtOAc (60 mL), washed with 1 M HCl (20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated to give crude compound 39A (59 mg) as a white solid that was used without further purification: m/z=534.3 (M+1).

Compound 39B:

A solution of compound 38B (49 mg, 0.919 mmol) and sodium methoxide (25% w/w in MeOH, 0.03 mL) in MeOH (1.25 mL) was heated to 55° C. with stirring. After 3.5 h the mixture was diluted with EtOAc (60 mL), washed with 1 M HCl (20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated to give crude compound 39B (49 mg) as a white solid that was used without further purification: m/z=534.4 (M+1).

Compound TX63481:

A solution of DBDMH (14.5 mg, 0.0507 mmol) in DMF (0.3 mL) was added to a 0° C. solution of compound 39A (all above obtained, ≤0.0919 mmol) in DMF (0.5 mL) with additional DMF (0.2 mL) used to complete transfer. The mixture was stirred at 0° C. for 2.5 h, pyridine (23 μL, 0.28 mmol) was added, the mixture was heated to 55° C. for 5.5 h, then cooled

to room temperature overnight. The reaction mixture was diluted with EtOAc (60 mL); washed with sodium sulfite (10% w/w, 10 mL), 1 M HCl (10 mL) and brine (10 mL); dried (Na_2SO_4); and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound TX63481 (35 mg, 72% from compound 38A) as a glassy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.08 (s, 1H), 3.72 (t, 1H, J=6.7 Hz), 2.54 (m, 1H), 1.56 (s, 3H), 1.52 (s, 3H), 1.25 (s, 3H), 1.18 (s, 3H), 0.95-2.08 (m, 21H), 0.93 (s, 3H), 0.92 (s, 3H), 0.87 (t, 3H, J=7.2 Hz), 0.85 (s, 3H); m/z=532.4 (M+1).

Compound TX63484:

DMF (1.0 mL) was added to a precooled (0° C.) vial containing DBDMH (13.6 mg, 0.0476 mmol) and 39B (all above obtained, ≤0.0919 mmol) and the mixture stirred at 0° C. for 2 h, then warmed to room temperature over 45 minutes. Pyridine (23 μL, 0.28 mmol) was added, and the mixture was heated to 55° C. for 21 h. The reaction mixture was diluted with EtOAc (50 mL); washed with sodium sulfite (10% w/w, 10 mL), 1 M HCl (10 mL) and brine (10 mL); dried (Na_2SO_4); and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound TX63484 (38 mg, 78% from compound 38B) as a white foam solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.12 (s, 1H), 3.53 (m. 1H), 2.69 (m, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.26 (s, 3H), 1.19 (s, 3H), 0.94 (s, 6H), 0.89 (s, 3H), 0.88-2.10 (m, 24H); m/z=532.4 (M+1).

Compounds 40A and 40B:

A solution of compound 32 (480 mg, 0.701 mmol) in THF (20 mL) was cooled to −78° C., and i-PrLi (0.7 M in pentane, 5 mL, 3.5 mmol) was added. The resultant mixture was stirred at −78° C. for 2 h, quenched by the addition of saturated NH_4Cl (20 mL), and warmed to room temperature over 30 minutes. The biphasic mixture was diluted with EtOAc (75 mL), washed with H_2O (50 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 40% EtOAc in hexanes) to give compounds 40A (261 mg, 51%) as a white solid, and compound 40B (236 mg, 40%) as a glassy solid.

Compound 41:

A solution of compound 40A (261 mg, 0.358 mmol), MOMCl (0.14 mL, 1.8 mmol) and i-Pr_2NEt (0.37 mL, 2.12 mmol) in CH_2Cl_2 (5 mL) was stirred at reflux for 16 h. The resultant mixture was diluted with EtOAc (70 mL), washed with 1 M HCl (50 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated. Due to incomplete conversion the residue was dissolved in CH_2Cl_2 (5 mL), and MOMCl (0.14 mL, 1.8 mmol) and i-Pr_2NEt (0.37 mL, 2.12 mmol) were added. The mixture was heated to reflux for an additional 17 h, cooled to room temperature, diluted with EtOAc (70 mL), washed with 1M HCl (25 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated to give crude compound 41 as a white foam solid that was used without further purification.

Compound 42:

TBAF (1 M in THF, 4.3 mL, 4.3 mmol) was added to a room temperature solution of compound 41 (all above obtained, ≤0.358 mmol) in THF (12.4 mL), and the mixture was heated to 50° C. for 23 h. The resultant mixture was concentrated to ~2 mL, loaded directly onto silica, and purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound 42 (162 mg, 83% from compound 40A) as a white solid.

Compound 43:

A mixture of compound 42 (162 mg, 0.298 mmol), NMO (113 mg, 0.965 mmol), 4 Å MS (296 mg) and CH_2Cl_2 (7.5 mL) was stirred at room temperature for 10 min, then TPAP (10.8 mg, 0.0307 mmol) was added in one portion. The resultant mixture was stirred for 1.5 h, concentrated to ~2 mL, loaded directly onto silica gel, and purified by flash chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound 43 (139 mg, 86%) as a glassy solid.

Compound 44:

A solution of sodium methoxide (25% w/w in MeOH, 0.55 mL) was added to a 0° C. suspension of compound 43 (139 mg, 0.257 mmol) in EtOCHO (1.4 mL). The resultant mixture was stirred at 0° C. for 1 h, warmed to room temperature for an additional 6 h, diluted with EtOAc (60 mL), washed with 1 M HCl (15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated to give crude compound 44 as a pale-yellow, glassy solid that was used without further purification.

Compound 45:

A solution of compound 44 (all above obtained, ≤0.257 mmol) and NH_2OH.HCl (24.6 mg, 0.354 mmol) in a mixture of EtOH (1.9 mL), H_2O (0.45 mL), and THF (0.58 mL) was heated to 55° C. for 6 h. A solution of HCl (4 M in 1,4-dioxane, 0.1 ml, 0.4 mmol) was added and heating continued for 3 d. The resultant mixture was diluted with EtOAc (50 mL), washed with 1 M HCl (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 60% EtOAc in hexanes) to give compound 45 (19 mg, 14% from compound 43) as a glassy solid.

Compound 46:

A solution of compound 45 (19 mg, 0.037 mmol) and sodium methoxide (25% w/w in MeOH, 0.01 mL) in MeOH (0.5 mL) was heated to 55° C. with stirring. After 6.5 h the mixture was diluted with EtOAc (50 mL), washed with 1 M HCl (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated to give crude compound 46 (19 mg) as a glassy solid that was used without further purification.

Compound TX63496:

DMF (1.0 mL) was added to a precooled (0° C.) vial containing DBDMH (6.0 mg, 0.021 mmol) and 46 (all above obtained, ≤0.037 mmol) and the mixture stirred at 0° C. for 2.5 h, then warmed to room temperature for 3.5 h. Pyridine (9 μL, 0.1 mmol) was added, the mixture heated to 55° C. for 18.5 h. The reaction mixture was diluted with EtOAc (40 mL); washed with sodium sulfite (10% w/w, 10 mL), 1 M HCl (10 mL) and brine (10 mL); dried (Na_2SO_4); and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 50% EtOAc in hexanes) to give compound TX63496 (12.3 mg, 65% from compound 45) as a white foam solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.09 (s, 1H), 3.38 (d, 1H, J=7.7 Hz), 2.55 (m, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 1.26 (s, 3H), 1.19 (s, 3H), 1.00-2.10 (m, 16H), 0.95 (s, 3H), 0.93 (s, 3H), 0.91 (d, 3H, J=6.6 Hz), 0.87 (s, 3H), 0.86 (d, 3H, J=6.6 Hz); m/z=518.4 (M+1).

All of the compounds, compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the disclosure may have only been described in terms of certain embodiments, it will be apparent to those of skill in the art that variations may be applied to the compounds, compositions and methods and in the steps or in the sequence of steps of the method described herein without departing

from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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The following references to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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SEQUENCE LISTING

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<220> FEATURE:
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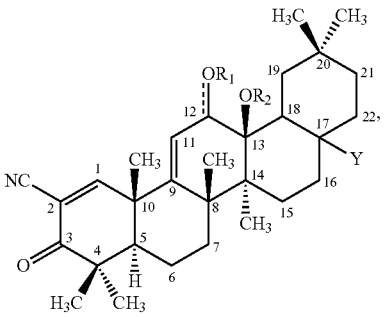
What is claimed is:

1. A compound of the formula:

(I)



wherein:

R_1 is hydrogen, $alkyl_{(C\leq 6)}$, $acyl_{(C\leq 6)}$, or absent when the oxygen atom to which it is bound forms part of a double bond;

R_2 is hydrogen, $alkyl_{(C\leq 6)}$, $acyl_{(C\leq 6)}$, a substituted version of either of the two latter two groups, or as provide for below; and

Y is:

hydrogen, hydroxy, halo, amino, cyano or mercapto;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkyl\text{-}amino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkyl\text{-}sulfonylamino_{(C\leq 8)}$, or substituted versions of any of these groups;

$-alkanediyl_{(C\leq 8)}\text{-}R_a$, $-alkenediyl_{(C\leq 8)}\text{-}R_a$, or a substituted version of any of these groups, wherein R_a is:

hydrogen, hydroxy, halo, amino, cyano or mercapto;

$heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $—OC(O)NH\text{-}alkyl_{(C\leq 8)}$, $—OC(O)CH_2NHC(O)O—alkyl_{(C\leq 8)}$, $—OCH_2\text{-}alkylthio_{(C\leq 8)}$, or a substituted version of any of these groups; or

R_a and R_2, taken together, are a covalent bond between one end of the $-alkanediyl_{(C\leq 8)}$- or $-alkenediyl_{(C\leq 8)}$- group and the oxygen atom attached to the carbon atom labeled 13; or

$—(CH_2)_mC(O)R_b$, wherein m is 0-6 and R_b is:

hydrogen, hydroxy, halo, amino, hydroxyamino, or mercapto;

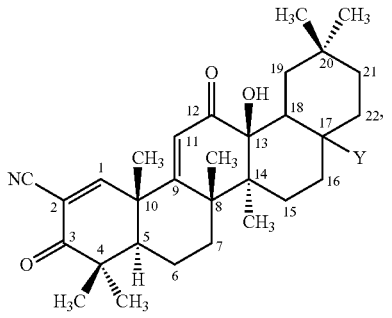
$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $hetero\text{-}aryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $alkyl\text{-}sulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, —NH-$heterocycloalkyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

R_b and R_2, taken together, are a covalent bond between the carbonyl of the $—(CH_2)_mC(O)—$ group and the oxygen atom attached to the carbon atom labeled 13, wherein m is 1;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, further defined as:

(II)



wherein Y is:

hydrogen, hydroxy, halo, amino, cyano or mercapto;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkyl\text{-}amino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkylsulfonyl\text{-}amino_{(C\leq 8)}$, or substituted versions of any of these groups;

$-alkanediyl_{(C\leq 8)}\text{-}R_a$, $-alkenediyl_{(C\leq 8)}\text{-}R_a$, or a substituted version of any of these groups, wherein R_a is:

hydrogen, hydroxy, halo, amino, cyano or mercapto; or

$heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkyl\text{-}amino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $—OC(O)NH\text{-}alkyl_{(C\leq 8)}—OC(O)CH_2NHC(O)O\text{-}alkyl_{(C\leq 8)}$, $—OCH_2\text{-}alkylthio_{(C\leq 8)}$, or a substituted version of any of these groups; or

$—(CH_2)_mC(O)R_b$, wherein m is 0-6 and R_b is:

hydrogen, hydroxy, halo, amino, hydroxyamino, or mercapto; or $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, —NH-$heterocycloalkyl_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein R_1 is hydrogen.

4. The compound of claim 1, wherein R_1 is $acyl_{(C\leq 6)}$.

5. The compound of claim 4, wherein R_1 is acetyl.

6. The compound of claim 1, wherein R_1 is absent and the oxygen atom to which it is bound forms part of a double bond, thereby resulting in an oxo group at the carbon atom labeled 12.

7. The compound of claim 1, wherein R_2 is hydrogen.

8. The compound of claim 1, wherein Y is substituted $alkyl_{(C\leq 8)}$.

9. The compound of claim 8, wherein Y is hydroxymethyl.

10. The compound of claim 1, wherein Y is $-alkanediyl_{(C\leq 8)}\text{-}R_a$.

11. The compound of claim 10, wherein Y is $—CH_2—R_a$.

12. The compound of claim 1, wherein R_a is hydroxy.

13. The compound of claim 1, wherein R_a is $acyloxy_{(C\leq 8)}$.

14. The compound of claim 13, wherein R_a is acetyloxy.

15. The compound of claim **1**, wherein Y is —$(CH_2)_mC(O)R_b$.

16. The compound of claim **15**, wherein m=0.

17. The compound of claim **15**, wherein R_b is $alkoxy_{(C\leq 8)}$.

18. The compound of claim **17**, wherein R_b is methoxy.

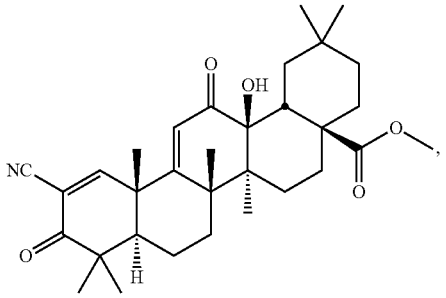
19. The compound of claim **17**, wherein R_b is ethoxy.

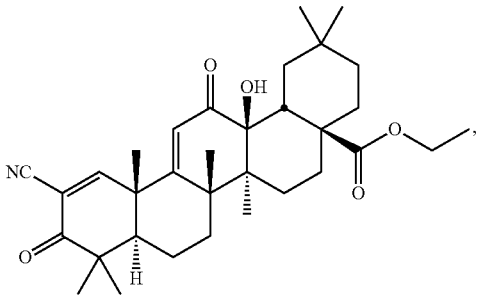
20. The compound of claim **15**, wherein R_b is amino.

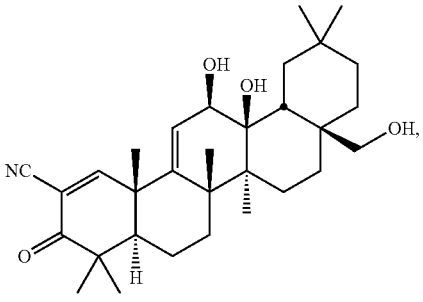
21. The compound of claim **15**, wherein R_b is $alkylamino_{(C\leq 8)}$.

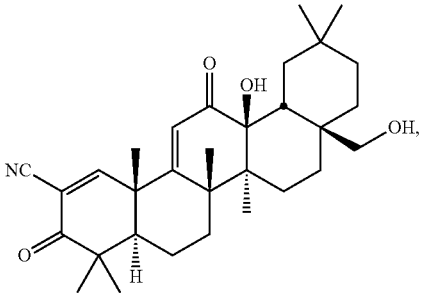
22. The compound of claim **21**, wherein R_b is ethylamino.

23. The compound of claim **1**, further defined as:









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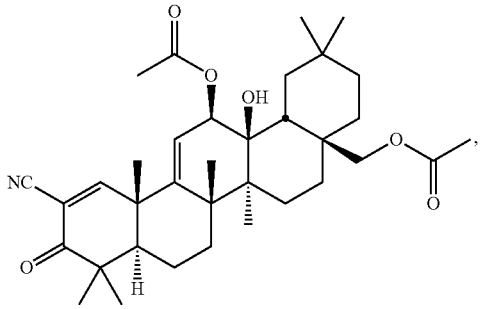

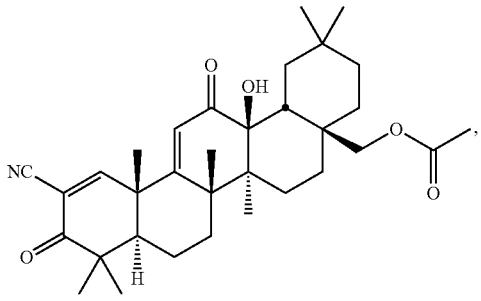

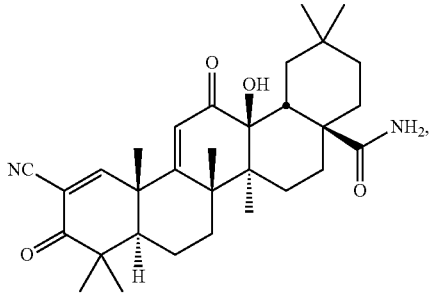

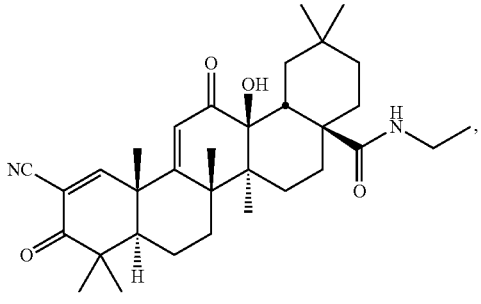

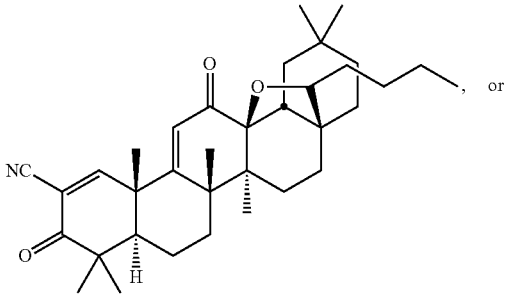

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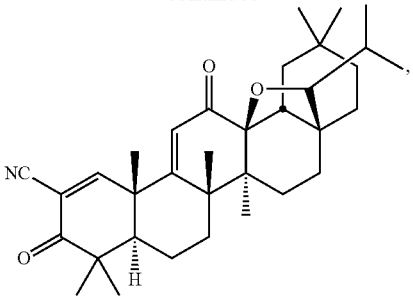

or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising:

a) the compound of claim **1**; and

b) an excipient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,278,912 B2
APPLICATION NO. : 14/023180
DATED : March 8, 2016
INVENTOR(S) : Xin Jiang, Christopher F. Bender and Melean Visnick

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claims

In claim 2, column 62, line 32, delete "alkenyloxy$_{(C\leq8)}$aryloxy$_{(C\leq8)}$," and insert --alkenyloxy$_{(C\leq8)}$, aryloxy$_{(C\leq8)}$,-- therefor.

In claim 2, column 62, line 35, delete "arylamino$_{(C\leq8)}$aralkylamino$_{(C\leq8)}$," and insert --arylamino$_{(C\leq8)}$, aralkylamino$_{(C\leq8)}$,-- therefor.

In claim 2, column 62, lines 37-38, delete "–OC(O)NH–alkyl$_{(C\leq8)}$–OC(O)CH_2NHC(O)O–alkyl$_{(C\leq8)}$," and insert -- –OC(O)NH–alkyl$_{(C\leq8)}$, –OC(O)CH_2NHC(O)O–alkyl$_{(C\leq8)}$,-- therefor.

Signed and Sealed this
Seventeenth Day of May, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office